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Health Technology Assessment Policy and Methods Review

HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning

March 2024

make history.

Title: Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning
Online ISBN: 978-0-9923968-1-7

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The combined work may be cited as:

Merlin T, Laka M, Carter D, Gao Y, Choi YS, Parsons J, Milverton J, Ellery B, Newton S, Hill H, Morona J, Kessels S, Tamblyn D. Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning. Canberra, ACT: Australian Department of Health and Aged Care, 2024.

Recommended citation for Paper 1:

Laka M, Carter D, Gao Y, Choi YS, Tamblyn D, Merlin T. *International health technology market approval, funding and assessment pathways*. In Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning. Canberra, ACT: Australian Department of Health and Aged Care, 2024.

Recommended citation for Paper 2:

Parsons J, Milverton J, Ellery B, Tamblyn D, Merlin T. *Horizon scanning and early assessment*. In Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning. Canberra, ACT: Australian Department of Health and Aged Care, 2024.

Recommended citation for Paper 3:

Newton S, Hill H, Tamblyn D, Merlin T. HTA Methods: Determination of Population, Intervention, Comparator, and Outcome (PICO). In Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning. Canberra, ACT: Australian Department of Health and Aged Care, 2024.

Recommended citation for Paper 4:

Tamblyn D, Morona J, Carter D, Kessels S, Merlin T. Clinical Evaluation Methods in HTA. In Health Technology Assessment Policy and Methods Review: HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning. Canberra, ACT: Australian Department of Health and Aged Care, 2024.

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GLOSSARY AND ABBREVIATIONS

These definitions have been developed based on existing definitions in the first instance, and where there is no universally accepted definition, they have been designed as a working definition for the purposes of this paper.

Term	Definition
AAWG	Appraisal Alignment Working Group (UK)
ACE	Agency for Care Effectiveness (Singapore)
ACIP	Advisory Committee on Immunization Practices (USA or Taiwan)
Added therapeutic value	A significant[1] improvement in population health outcomes obtained with a new medicine or technology when compared to the best available therapeutic alternatives. [1] 'Significant' means a clinically important improvement in health outcomes. It is not demonstrated solely by a statistically significant difference in health outcomes.
Advanced therapy medicinal products (ATMP)	Medicines based on genes, tissues or cells that treat often very rare and severe disease or conditions. Also known as highly specialised therapies or technologies, innovative treatments or biologics.
AHMAC	Australian Health Ministers' Advisory Council
AHRQ	Agency for Healthcare Research and Quality (USA)
AHTA	Adelaide Health Technology Assessment
AIFA HSS	Italian Medicines Agency Horizon Scanning System
AIHTA	Austrian Institute for Health Technology Assessment
AMNOG	Arneizmittelmarkt- Neuordnungsgesetz (Germany). A law reforming the pharmaceutical market to include reimbursement followed by early benefit assessment.
AMR	Antimicrobial resistance
ANZHSN	Australia and New Zealand Horizon Scanning Network
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical
ATAGI	Technical Advisory Group on Immunisation
AWMSG	All Wales Medicines Strategy Group
AWTTC	All Wales Therapeutics and Toxicology Centre
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices; Germany)
C2H	Center For Outcomes Research And Economic Evaluation For Health (Japan)
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CDC	Centers for Disease Control and Prevention (in USA) Centre for Disease Control (in Taiwan)
CDE	Center for Drug Evaluation (Taiwan)
CEA	Cost-effectiveness analysis
CED	Coverage with evidence development
CEMIPP	Cost-Effectiveness Methodology for Immunisation Programmes and Procurement working group (UK)
CGP	Comprehensive genomic profiling
Codependent technology	A medical technology or service that relies on another technology to achieve its intended purpose or enhance its effect. The most common type is a test-medicine pair. The testing component is otherwise known as a companion diagnostic or CDx. The medicine component is otherwise known as precision medicine, targeted medicine, or stratified medicine.

	The submission for a public funding decision must show the net clinical benefit of the joint use of the technologies i.e. the test/medicine pair
Conditional marketing authorisation	Provided by the EMA for medicines that address unmet medical need (granted with less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risks inherent in the fact that more data are required)
COS	Core Outcome Set - a minimum set of outcomes that should be measured and reported in all clinical trials undertaken in a specific health condition, that are considered clinically relevant.
CoV	Committee on Vaccinations (the Netherlands)
Coverage with evidence development (CED)	Early funding of a health technology conditional on gathering additional evidence to address the sources of uncertainty. (Also called access with evidence development.) [1]
CSCQ	Committee for Scientific Consistency & Quality (for Joint Clinical Assessments undertaken by EUnetHTA)
CTV	Technical Vaccination Committee (Comité Technique des Vaccinations) of the HAS
CUA	Cost-utility analysis
CVZ	Health Care Board (College voor zorgverzekeringen) (The Netherlands)
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment
DCEA	Distributional Cost-Effectiveness Analysis
Department (the)	Australian Government Department of Health and Aged Care
DHI	Dutch Health Institute
DoH	Department of Health and Social Care (UK)
EAMS	Early Access to Medicines Scheme (Scotland)
Early awareness and alert (EAA) system	A system that aims to identify, filter and prioritise new and emerging health technologies, or new uses of existing interventions; to assess or predict their impact on health, health services and/or society; and to disseminate information. [1]
Early scientific advice / early dialogue	Scientific advice (or early dialogue process) is non-binding advice offered by regulators and/or HTA agencies to companies developing medicines and, increasingly, devices and diagnostics. The advice is aimed at improving the quality and appropriateness of the data produced by the developers (e.g. clinical trials) in view of future regulatory and HTA assessment. This may also involve early data synthesis. In some countries, it is conducted as a fee-for-service.
Early value assessment	A coverage with evidence development process initiated by NICE in the UK for medical devices, digital therapies and diagnostics. It has specific criteria for which technologies are eligible. Technologies must have regulatory approval.
Early value proposition, sometimes called early HTA	Economic analysis early in a technology's lifecycle - 'as early as feasible' concept. Mainly used to inform the commercial or business strategies of the pharmaceutical industry.
Early warning system	A stable organisational unit with reliable connections and sources which aims to: identify new technologies that have the potential to make a large impact on health services; filter and prioritise these technologies to select those most likely to have an impact on health, services and budgets; and assess that impact. [1]
ECRI	Economic Cycle Research Institute
EEFA	Ethics, equity, feasibility and acceptability
EMA	European Medicines Agency
Emerging health technology	A health technology that has not yet been adopted within the healthcare system. [1]
Emerging technologies	See "emerging health technology"
EQ-5D	EuroQol 5 Dimension
ESC	Economic sub-committee (of the PBAC; Australia)
EU	European Union
EUnetHTA	European Network of Health Technology Assessment
Exceptional circumstances	EMA marketing authorisation granted when the applicant in unable to provide comprehensive data, because the condition to be treated is rare, or because collection of full information is not possible or is unethical

FDA	Food and Drug Administration (USA)
FMEC	CADTH's Formulary Management Expert Committee (Canada; excluding Quebec)
G-BA	The Federal Joint Committee (Gemeinsamer Bundesausschuss) (Germany)
GR	Gezondheidsraad (The Netherlands)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de Santé (France)
HCP	Healthcare practitioner
HealthPACT	Health Policy Advisory Committee on Technology
High unmet clinical (medical) need	A severe or life-threatening condition for which there exists no or very limited diagnostic or treatment options [2]
Highly specialised technologies (therapies)	See advanced therapy medicinal products
HIQA	Health Information and Quality Authority (Ireland)
HIRA	Health Insurance Review and Assessment Service (South Korea)
HIS	Healthcare Improvement Scotland
Horizon scanning (HS)	The systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to affect health, health services and/or society. [1]
HPRA	Health Products Regulatory Agency (Ireland)
HR-QoL	Health related – quality of life
HST	Highly specialised technology
HTA	Health Technology Assessment
HTW	Health Technology Wales
ICER	Incremental cost-effectiveness ratio Institute for Clinical and Economic Review (USA)* Referred to as US ICER in text.
IHE	Institute of Health Economics (Alberta, Canada)
i-HTS	International HealthTechScan, formerly Euroscan
ILAP	Innovative Licensing and Access Pathway (United Kingdom)
INAHTA	International Network of Agencies for Health Technology Assessment
INESSS	Institut national d'excellence en santé et services sociaux (Canada)
IO	Innovation Observatory (UK)
IOM	International Organisation for Migration
IPD	Individual patient data
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany)
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparisons
JCA	Joint Clinical Assessment (Europe)
JCVI	Joint Committee on Vaccination and Immunisation
JSC	Joint Scientific Consultations (provided by the EMA, in Europe)
KACIP	Korea Advisory Committee on Immunization Practices
KCDC	Korea Disease Control and Prevention Agency
KCE	Belgian Health Care Knowledge Centre
KECIP	Korea Expert Committee on Immunisation Practices
KFDA	Korea Food & Drug Administration
LSDP	Life Saving Drug Program (Australia)
MaHTAS	Malaysian Health Technology Assessment Section
MAIC	Matching-adjusted indirect comparisons
Managed Entry (Access)	A conditional arrangement between a manufacturer and payer that enables earlier reimbursement of a health technology to address uncertainty in its performance or to manage its utilisation[1].

MAUI	Multi-attribute utility instrument
MBS	Medicare Benefits Schedule (Australia)
MCDA	Multiple criteria decision analysis
MCID	Minimum clinically important difference
'Me-too' medicine	A medicine that is structurally related to a first-in-class medicine i.e., belonging to the same therapeutic class as the first-in class medicine and indicated for the same therapeutic purposes [3].
MoHW	Ministry of Health and Welfare (South Korea)
MPC	Molecular Pathology Consortium (Scotland)
MS	Member States (of EUnetHTA, i.e., individual countries in Europe)
MSAC	Medical Services Advisory Committee (AUS)
MTC	Mixed treatment comparisons
NACI	National Advisory Committee on Immunisation (Canada)
NECA	National Evidence-based healthcare Collaborating Agency (South Korea)
New health technology	A health technology that is in the launch, early post-market or early diffusion stages. [1]
NHS	National Health Service (United Kingdom)
NHSU	National Horizon Scanning Unit
NICE	National Institute for Health and Care Excellence (UK)
NIHR	National Institute for Health Research (UK)
NIHTA	National Institute for Health Technology Assessment (Taiwan)
NIP	National Immunisation Program (Australia)
NIPH	Norwegian Institute of Public Health
NIPH NO	Nordic Medicines Agency
NITAGs	National Immunization Technical Advisory Groups
NMA	Network meta-analysis
NPF	Nordic Pharmaceutical Forum
NTFEP	New Technology Funding Evaluation Program
OH	Ontario Health
Orphan designation	TGA designation for a medicine intended for the treatment or prevention of a disease that is life-threatening or seriously debilitating, with a prevalence in the Australia of less than 5 in 10,000, or where the marketing of the medicine is not likely to be financially viable to justify the investment for its development, and where the application is for only one patient indication
OS	Overall survival
PASC	PICO confirmation sub-committee (of the MSAC; Australia)
PBAC	Pharmaceutical Benefits Advisory Committee (AUS)
PBCAC	The Pharmaceutical Benefit Coverage Assessment Committee (South Korea)
PBS	Pharmaceutical Benefits Scheme (Australia)
PCC	Participant, Concept, Context
PCORI	Patient-Centered Outcomes Research Institute
PFS	Progression-free survival
PHAC	Public Health Agency of Canada
PICO	Population, Intervention, Comparator, Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROs / PROMs	Patient Reported Outcomes / Measures
PSD	Public Summary Document (Australia)
QALY	Quality-adjusted life years
QBA	Quantitative bias analysis
QoL	Quality of life

QPACT	Queensland Policy Advisory Committee on Technology
RCT	Randomised controlled trial
Real world data (RWD)	Data collected during the routine delivery of health care
Real world evidence (RWE)	Evidence derived from the analysis of real-world data (see above)
RedETS	Spanish Network of Health Technology Assessment Agencies
RWEE	Real world evidence of effectiveness
SAPACT	South Australia Policy Advisory Committee on Technology
SINETIS	Topic Identification and Filtration System for Spain's Early Detection and Awareness Methods
SMC	Scottish Medicines Consortium
STA	Single-technology appraisal
STC	Simulated treatment comparisons
STIKO	Standing Committee on Vaccination (Germany)
TGA	Therapeutic Goods Administration (AUS)
The Department	Department of Health and Aged Care (Australia)
UK	United Kingdom
US	United States
US ICER	US Institute for Clinical and Economic Review
USA	United States of America
VEG	Vaccine evaluation group
VPACT	Victoria Policy Advisory Committee on Technology
WAPACT	Western Australia Policy Advisory Committee on Technology
WHO	World Health Organisation
ZIN	Zorginstituut Nederland (the Netherlands)

BACKGROUND

Health technology assessment (HTA) is a term used to describe the methods and activities for robustly establishing the value of a health technology by estimating the comparative benefits, harms and cost implications for a payer, decision maker or jurisdiction. A health technology is defined as an intervention developed to prevent, diagnose, or treat medical conditions; promote health; provide rehabilitation; or organise healthcare delivery. The intervention can be a test, device, medicine, vaccine, procedure, program, or system [1].

The Australian Government has an extensive history of utilising HTA within its decision-making processes in both regulatory and reimbursement settings. Key Australian national HTA bodies include the Therapeutic Goods Administration (TGA), the Pharmaceutical Benefits Advisory Committee (PBAC) and its subsidiary committees, and the Medical Services Advisory Committee (MSAC) and its subsidiary committees.

The purpose of the HTA Policy and Methods Review ('the HTA Review') is to: broadly examine the methods and policies relating to HTA as they are applied in the literature or in comparable international jurisdictions, compare these processes with those used in the Australian setting, and outline the possible implications of adopting changes in the Australian HTA landscape.

The focus is specifically on HTA policy and methods concerning:

1. all medicines and vaccines
2. highly specialised therapies (such as cell and gene therapies)
3. other health technologies (for example a pathology test or an imaging technology) that improve health outcomes associated with the technologies indicated above
4. foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.

The HTA Review Reference Committee formulated questions on specific topics for independent research. Adelaide Health Technology Assessment (AHTA) was contracted to address four of these topics, each containing several research questions. One paper for each of the four topics was drafted and made publicly accessible at the end of 2023. This report compiles each of the four papers into a single volume, with a methodology section shared across all topics, and results presented in separate chapters of the report. Feedback from public consultation, that addressed the content of these original draft papers, was also collated and summarised.

RESEARCH TOPIC

Adelaide Health Technology Assessment addressed the following four research topics in four separate papers. Each research topic was accompanied by detailed sub-topics.

PAPER 1: INTERNATIONAL HEALTH TECHNOLOGY MARKET APPROVAL, FUNDING AND ASSESSMENT PATHWAYS

Sub-Topic: International Regulatory and reimbursement/HTA pathways

- Pathways for registration and reimbursement of health technologies internationally, including:
  a) overall health system and societal context
  b) overall steps, processes and timings for these pathways, including prioritisation, flexibility, certainty, transparency, and communication with stakeholders
  c) alignment between registration and reimbursement processes and evaluations (particularly for parallel and/or priority assessments)
  d) alignment and differences between evaluations for different types of technologies
  e) involvement of different stakeholders in these approaches.

Sub-Topic: Special pathways and/or equity considerations for specific types of technologies and/or patient groups

- Overview and comparison of special pathways used internationally for:
  a) technologies for rare diseases or for small patient sub-populations / ultra-rare mutations.
  b) populations for which there is a high unmet clinical need
  c) vulnerable and/or disadvantaged patient populations
  d) technologies with uncertain long-term outcomes
  e) co-dependent technologies
  f) antimicrobials
  g) new 'advanced', high-cost therapies (e.g. cell and gene therapies)
  h) technologies/indications where there is no current sponsor/application (e.g. repurposing of listed medicines or unlisted medicines for very small populations)
  i) any other types of technologies.
- Involvement of different stakeholders in these approaches (including consumers, clinicians, industry and academia).
- Applicability to the Australian context.

Sub-Topic International HTA Reforms

- Reforms implemented or proposed in recent years, and their outcomes.
- Overview of HTA systems in international jurisdictions that have managed and adapted with rapid technological change.

Sub-Topic: Benefits, risks, limitations and ethical considerations associated with different approaches, as identified in academic and other literature.

PAPER 2. HORIZON SCANNING AND EARLY ASSESSMENT

Sub-Topic: Horizon Scanning for emerging health technologies

- Approaches to horizon scanning in Australia and internationally for early identification of:
  a) new types of health technologies which may require reconsideration of existing funding, HTA and/or service delivery arrangements
  b) new health technologies for early assessment (i.e. potentially 'transformative' technologies which may address a high unmet clinical need and likely to have a significant cost impact).
- Involvement of stakeholders (including consumers, clinicians, industry and academia) in these approaches.
- How horizon scanning information is used.
- Approach to HS for vaccines
- Benefits, risks and limitations of these approaches.
- Applicability of international approaches to the Australian setting.

Sub-Topic: Early assessment of new health technologies

- Approaches to early value proposition, early scientific advice and early value assessment (as an example of coverage with evidence development) used in comparable jurisdictions and/or outlined in the academic literature, including:
  a) involvement of stakeholders including consumers
  b) what/how technologies are selected for assessment
  c) assessment methodology
  d) equity considerations
  e) how information is used (e.g., triaging applications to facilitate early access, by triggering a priority pathway facilitating coordination of future steps in regulatory and reimbursement pathways, or setting mutual expectations regarding potential funding and pricing, and any future steps and information requirements).
  f) Benefits, risks, and limitations of these approaches

PAPER 3. HTA METHODS: DETERMINATION OF POPULATION, INTERVENTION, COMPARATOR, AND OUTCOME (PICO)

Sub-Topic: Determination of PICO

- Policies and processes used in Australia and internationally, including:
  a) involvement of sponsors, consumers, clinicians, regulatory agencies, advisory bodies, and other relevant stakeholders, including involvement in determining PICO.
  b) definition and equity considerations regarding treatment population(s) of interest, including relevant sub-populations and those determined by codependent testing, as well as populations defined by molecular biomarkers (for molecular/tissue-agnostic indications).
  c) selection of comparator(s)
  d) determination of outcomes of interest.
- Special considerations / approaches for determination of PICO, for:
  a) technologies for rare diseases or for small patient sub-populations / ultra-rare mutations
  b) populations for which there is a high unmet clinical need
  c) vulnerable and/or disadvantaged patient populations
  d) technologies with uncertain long-term outcomes
  e) codependent technologies

Sub-Topic: Recent reforms

- Recent changes to pre-assessment processes in Australia and internationally
  a) extent that they align with change in the types of health technologies
  b) outcomes of reforms, including benefits, risks, and limitations, as identified in the literature.

PAPER 4. HTA METHODS: CLINICAL EVALUATION

Sub-Topic: Clinical Evaluation methodology

- Approaches used in Australia, and internationally to clinical evaluation including on the use of different types of evidence (including non-randomised studies, observational evidence, and non-peer reviewed data) and consumer evidence considered for:
  a) evaluation of clinical effectiveness and safety
  b) other aspects of the evaluation, including identifying the patient population(s), pathway and treatment algorithm, identifying long-term adverse events, and assessing equity considerations.
- Strengths and limitations of HTA by multiple committees,
- Approaches used in Australia, and internationally+ for the weighting of benefits.

Sub-Topic: Special considerations for particular technology or population types

a) Technologies for rare diseases / for small patient populations, where data can be limited.
b) Populations for which there is a high unmet clinical need.
c) Other equity considerations, including vulnerable and disadvantaged populations.
d) Co-dependent technologies.
e) Emerging technologies associated with limited knowledge of long-term outcomes, and rapid changes in the evidence base that may make evaluations out of date relatively quickly.

Sub-Topic: Recent reforms

- Recent changes to clinical evaluation processes and methodology in Australia and internationally
  a) Extent that they align with change in the types of health technologies
  b) Outcomes of reforms, including benefits, risks, and limitations, as identified in the literature.

Notes:

Health technologies of interest are those that are within the scope of the HTA Policy and Methods Review, as per the Terms of Reference.

"Comparable jurisdictions" or "international jurisdictions" relates to comparable international jurisdictions of interest as determined by the Reference Committee.

METHODS

OVERVIEW

A scoping review approach was used to address the research topics. This approach had defined steps, including identifying and selecting studies, extracting the findings, collating and summarising the results and consulting with stakeholders.

A scoping review, in the context of the HTA Review, was intended to examine the range and nature of current methods, processes, policies and research associated with the research topic. The aim being to synthesise information from a broad range of sources, including scientific literature, HTA databases and HTA agency websites and reports. During the data collation step of the project, an adaptive approach was applied to ensure the information was pertinent, while balancing the competing priorities of comprehensiveness and timeliness. As is consistent with scoping review methodology, an adaptive and iterative approach, that refines the inclusion and consideration of evidence, was key to ensuring the most relevant information was identified.

HTA experts (both national and international) were contacted to provide perspectives from their local region on each of the topics of the papers, and to clarify findings, when required.

The findings from the scoping reviews, correspondence with HTA experts and input from the first public consultation process were analysed in terms of the implications (risks, benefits, limitations) to the Australian health care system of adopting alternative HTA policies, pathways or processes. Where possible, options for facilitating access to medicines more rapidly and potentially providing solutions to contemporary HTA issues were presented to inform the Options Paper that was developed by the Reference Committee to present to the Department of Health and Aged Care ('the Department'). These options were grounded both in the evidence base and in HTA expert opinion.

Information obtained from the public / stakeholder consultation on the four draft papers and the Options Paper, facilitated by the Department as part of the HTA Review, was analysed, summarised, and incorporated into this final combined evidence-based report.

Scoping review approach

The scoping review followed the broad framework described by Arksey and O'Malley (2005)[4], and extended upon by multiple experts (Levac et al (2010)[5], Peters et al (2020)[6], Peters et al (2021)[7], and Khalil et al (2022)[8]. The scoping review approach contains six steps:

- Identifying the research question (using the 'participants, concept, context' (PCC) approach)

- Identifying relevant studies
- Study selection
- Charting the data
- Collating, summarising and reporting results
- Consultation

[from Arksey and O'Malley, 2005 [4]].

These steps are described in greater detail below. Reporting of the methods and results of the scoping review was informed by the PRISMA-ScR checklist (modified checklist for scoping reviews)[9].

IDENTIFYING THE RESEARCH QUESTION

The research topics developed by the Reference Committee are given in the previous section. The concepts and context associated with these were extracted to inform the literature search and criteria for including evidence for the scoping review. When summarising and discussing the findings of the included evidence, the full research topic was considered.

Table 1 Participants, Concepts, Context (PCC) domains for the scoping review

	Participants	Concepts	Context
Paper 1	Australian and International participants in HTA: Decision-makers; HTA experts and evaluators; citizens; consumers; industry.	International and national processes, pathways and frameworks for the conduct of HTA, including alignment with regulatory processes, involvement of different stakeholders, and current reforms. Variations in processes for specific technologies or populations* (equity considerations).	Health technology assessment in developed economies and jurisdictions with similar health care systems. The focus is on HTA relating to: • medicines and vaccines, • highly specialised therapies (such as cell and gene therapies), • companion technologies associated with the technologies above (ie codependent technology pairs) • foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.
Paper 2	Australian and International participants in HTA: Decision-makers; HTA experts and evaluators; citizens; consumers; industry.	Methods and processes used for horizon scanning and early assessment, including involvement of stakeholders. Uses of horizon scanning (objectives and applications). Target technologies of horizon scanning and early value assessment.	Health technology assessment in developed economies and jurisdictions with similar health care systems. The focus is on horizon scanning and early value assessment relating to: • medicines and vaccines, • highly specialised therapies (such as cell and gene therapies), • companion technologies associated with the technologies above (ie codependent technology pairs) • foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-

			effectiveness of new health technologies.
Paper 3	Australian and International participants in HTA: Decision-makers; HTA experts and evaluators; citizens; consumers; industry.	Policies, methods and conventions for determining Populations, Interventions, Comparators and Outcomes (PICO) in HTA. Involvement of stakeholders for determining PICO elements. Variations in the methods for determining the PICO for specific technologies or populations*.	Health technology assessment in developed economies and jurisdictions with similar health care systems. The focus is on HTA pre-assessment relating to: • medicines and vaccines, • highly specialised therapies (such as cell and gene therapies), • companion technologies associated with the technologies above (i.e. codependent technology pairs) • foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.
Paper 4	Australian and International participants in HTA: Decision-makers; HTA experts and evaluators; citizens; consumers/patients; industry.	Methods used in HTA for including and evaluating different (non-traditional) types of evidence, and any variations applied for specific technologies or populations*. Methods for weighting benefits. Methods for incorporating consumer evidence and current reforms.	HTA in developed economies and jurisdictions with similar health care systems. The focus is on HTA relating to: • medicines and vaccines, • highly specialised therapies (such as cell and gene therapies), • companion technologies associated with the technologies above (i.e. codependent technology pairs) • foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.

*Specific technologies or populations are presented in full in Research Topic section.

HTA = Health technology assessment.

IDENTIFYING RELEVANT EVIDENCE

Evidence was identified from the following sources:

- PubMed
- Embase
- International HTA database
- HTA Agency websites (NICE, CADTH, etc are listed in Appendix 2)
- Additional sources as recommended during consultation with experts
- Forward citation mining (sometimes called snowballing) and backward citation mining (sometimes called pearling).

Bibliographic databases

An initial broad search for HTA frameworks, methods and processes was conducted (Search 1), along with a specific search for horizon scanning and early assessment

methods and processes (Search 2). Subsequent targeted searches and citation mining were applied to increase the breadth of information for each paper, where required.

A pilot search conducted in PubMed and identified that there was a lack of MeSH terms that were likely to be sensitive enough while maintaining a reasonable yield of relevant literature. Searching only the MeSH term for heath technology assessment ('technology assessment, biomedical') was unlikely to be broad enough and would miss other aspects of decision making in health care or health care resourcing. Using MeSH terms higher in the hierarchy than "technology assessment, biomedical" resulted in large numbers of articles and very low specificity for the purpose of this review. After many iterations an appropriate balance of sensitivity and specificity in search yield was obtained.

The final search strategies are given in Appendix 1.

Search filters

The publication date range for Search 1 (for Paper 1, Paper 3 and Paper 4) was limited to 1/1/2018 onwards, capturing the most recent 5 years of publications. This date range is consistent with the focus of the scoping review, which is the identification of the most relevant and up-to-date methods and processes used across relevant jurisdictions. To ensure that key documents (that remain relevant) published prior to 2018 were captured, we applied backward citation mining to selected documents to identify additional reports published within the last 10 years.

The publication date range for Search 2 (for Paper 2) was limited to 1/1/2000 onwards. This represents a 23-year span and reflects the slow rate of change in terms of approaches for some aspects of horizon scanning.

Searches were limited to English language articles.

Citation mining

To ensure the search conducted was comprehensive, forward and backward citation mining was selectively used to identify the methods and guidance reports used in the generation of a HTA.

Grey literature

The search for relevant information included a search of grey (unpublished) literature. Pragmatic and targeted searches (typically motivated by other included evidence) using an internet browser were conducted to identify literature or reports of health technology assessment processes. These include searches of the:

International HTA database

The authors searched the HTA database (https://database.inahta.org/) for methods and process documents relating to the conduct of HTA across jurisdictions with similar health care systems as Australia. Selected recent HTA reports of technologies (particularly technologies that are: novel; for rare diseases; used in vulnerable groups; used in combination with tests; anti-microbials; and, high-cost) were scanned to determine the methods and processes guides that were used in constructing those reports.

International Network of Agencies for Health Technology Assessment (INAHTA) and key jurisdiction search

A search of the websites belonging to INAHTA member agencies was performed to identify guidance and methods documents that included information on current HTA pathways, policies and processes. INAHTA member agencies are generally public sector, not-for-profit agencies with a direct link to regional or national government. The HTAs conducted, and the HTA methods and policies used, were therefore most likely to be relevant to the focus of the HTA Review. Information that was available on the websites of INAHTA agencies that was relevant to the scoping review, but that was not available as a downloadable document, was captured and included as relevant source documentation. Where it was identified from the INAHTA agency websites that process related information was located on alternative websites (such as regulatory websites or government websites), a targeted search for these documents was undertaken.

The initial search encompassed all INAHTA agencies that are not on the OECD low- or middle-income country list (given those health care systems may be less applicable to the Australian setting). On advice from the Reference Committee, greater emphasis was afforded to the following jurisdictions:

- United Kingdom
- Canada
- Europe (as a single jurisdiction)
- Germany
- France
- Netherlands
- Taiwan
- South Korea
- USA

Only documents available in English were retrieved. Time constraints meant that documents could not be translated. The full list of INAHTA agencies and the websites searched are included in Appendix 2.

Many jurisdictions did not have information available that was in English. The scoping review of bibliographic databases mitigated this to some extent as often many jurisdictions had research or methods papers published in English in peer reviewed journals. However, in some journal articles the information provided may not reflect recent changes in HTA processes, and so key informants were also targeted in a range of jurisdictions to provide local information on HTA methods and policies.

EVIDENCE SELECTION

The selection of articles and reports for inclusion in the scoping review was based on the relevance to the research topic, as focused by the Participants, Concepts, Context (PCC) criteria (Table 1).

Three experienced staff were allocated to the search results for each of the papers and screened the literature. The project teams for each paper then met to discuss the eligibility of different articles and technical reports using the PCC. During the evidence selection process, the teams met regularly to ensure consistency of the application of eligibility criteria and to decide on additional targeted searches. The search results were screened based on title and abstract within Rayyan[1]. Potentially relevant citations had their full text retrieved and were screened within an Endnote database (version X9.3.3).

Upon identification of an article or technical report, the authors determined whether the information was relevant, and it was catalogued for data extraction. Evidence that was clearly not relevant was excluded. When searching grey literature and agency websites, a record of the search (Date of search, Jurisdiction, Website, Organisation, Date of report, Language, Focus of document, Title of document, Eligibility for Papers (P1, P2, P3, P4)) was recorded. The cataloguing of identified studies provided transparency of the eligibility process and permitted the generation of a PRISMA flowchart, adapted for Scoping Reviews.

Identified grey literature was catalogued in a way that permitted a search for any updates of the literature prior to data extraction.

CHARTING THE DATA

Data extraction tables were developed and adapted to the research topic and were piloted on several articles and reports before the full data extraction commenced. The detailed country profiles are provided as Supplementary Data to this report (Attachment 1).

[1] https://www.rayyan.ai/

Collating, summarising and reporting the results

Collating

Matrices were developed to tabulate the different characteristics of HTA processes, frameworks, horizon scanning, methods for determining the PICO and broad clinical methods, by jurisdiction.

The characteristics that were captured for Paper 1 included:

- Health system characteristics (method of funding and health care delivery etc)
- Steps included in HTA pathways
- Timing of key milestones in the HTA pathways
- Use of prioritisation and disinvestment in pathways
- Flexibility of the process (and how it is achieved)
- Certainty or predictability of the process (and how it is achieved)
- Transparency of the process (and how it is achieved)
- Involvement of stakeholders (how, and when are they involved)
- Alignment between regulatory and reimbursement processes
- Whether different processes or pathways are used for different/specific technologies and populations

In addition, separate pathways for specific technologies (considering the key elements (if applicable) described above) were identified and described:

- Rare diseases / rare mutations or small populations
- Populations with high unmet clinical need
- Disadvantaged populations
- Technologies with uncertain / long term outcomes
- Codependent technologies
- Antimicrobials
- New, high-cost therapies (e.g., cell and gene therapies)
- Technologies without a current sponsor (e.g., re-purposing technologies for small populations).

The characteristics that were captured for Paper 2 included:

- Timing and governance (including resourcing) for performing horizon scanning and early assessment (including the involvement of stakeholders)
- Types of technologies included in horizon scanning reports
- Methods used for horizon scanning (including what is considered in horizon scanning and early assessments)
- Key focus or purpose of horizon scanning. How information is used (e.g., planning service delivery, early engagement with stakeholders, early engagement with industry / sponsors, pre-technology discussions relating to funding and pricing, identifying evidence limitations that could be addressed, informing subsequent

approach to regulatory, HTA and HTA pathways, identifying key risks in implementation, identifying gaps in current health care provision).

The characteristics that were captured for Paper 3 included:

- The involvement of stakeholders in determining elements of the PICO (e.g., what stakeholders, and how are they involved).
- The identification and considerations of subpopulations, populations determined by testing, and populations defined by molecular biomarkers, including any equity considerations that may arise.
- The conventions or policies regarding the selection of the comparator or comparators.
- The conventions or policies regarding the selection of outcomes of interest.
- Any variations to the PICO process or policies for:
    - Technologies for rare diseases or for small populations
    - Populations with high unmet clinical need
    - Vulnerable or disadvantaged patient populations
    - Codependent technologies
    - Emerging technologies with limited knowledge of long-term outcomes.
- Nature and impact of recent reforms to the processes or conventions for determining the PICO for HTA.

The characteristics that were captured for Paper 4 included:

- Evaluation of different types of evidence for clinical effectiveness and safety, including (but not limited to) the evaluation of:
    - Non-randomised studies
    - Observational evidence
    - Non-peer reviewed data
    - Consumer evidence
- Evaluation of methods applied to other aspects of the evaluation, including:
    - Identifying the patient pathway (treatment algorithm)
    - Identifying long term adverse events
    - Assessing equity considerations
- Evaluation of methods used for weighting of benefits (distributional and equity concerns)
- Evaluation of methods for particular technologies or populations
    - Technologies for rare diseases / rare mutations or small populations
    - Populations for which there is a high unmet clinical need
    - Equity considerations for vulnerable and disadvantaged populations
    - Co-dependent technologies
    - Emerging technologies with limited knowledge of long-term outcomes, or methods to deal with rapid changes in the evidence base
- Nature and impact of recent reforms in methods for evaluating methods including:

- How recent reforms align with recent changes in technologies
- Outcomes of reforms

Summarising

Following the extraction of high-level characteristics or elements relevant to the research topics, a summary judgement table was provided that indicated whether the HTA method or process (i.e. the categories described above for the four papers): fully met or was compliant with that element, was partially compliant, was not at all addressed, or it was not reported. A traffic light system (green, orange and red) was used so that this could be seen at a glance. The text summarised the reasons for why these judgements were made and justified was provided based on the evidence available. Processes and methods that were found to fully (or partially, where there was no full compliance) address these elements have been discussed in greater detail.

CONSULTATION

Consultation occurred throughout the development of this paper. Consultation was undertaken with the members of the HTA Review Reference Committee, the secretariat supporting the Review, key Committee members and Government employees involved in the provision of HTA in Australia, representatives from Medicines Australia industry working groups, and information gathered from international experts in HTA. Experts that were consulted have been named in the Acknowledgements section of this paper.

National and International experts

Consultation with multiple national and international HTA experts was undertaken, as required, to ascertain additional information or clarification on activities that may not have been published.

Australian consultation

Experts from the Department who are involved in the HTA process were consulted. Experts were experienced in PBAC, MSAC or TGA processes and methods, and included public servants and committee members. In addition, a workshop was held with representatives from the pharmaceutical industry (Medicines Australia working groups) and a separate workshop was held with the independent academic HTA groups that conduct evaluations of submissions to the PBAC for the funding of medicines, vaccines and highly specialised technologies.

HTA Review Consultation

As part of the HTA Review, AHTA received consultation feedback submitted to the Department from a range of stakeholders, including, amongst others, industry, the

public, clinicians, jurisdictional governments, HTA evaluators and HTA committee members.

Paper 1: International Health Technology Market Approval, Funding and Assessment Pathways

Health Technology Assessment Policy and Methods Review Papers

March 2024

International Health Technology Market Approval, Funding and Assessment Pathways

Paper 1 in Health Technology Assessment Policy and Methods Review Papers

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Acknowledgements

We would like to thank the following people who took the time to assist the team at AHTA, provided slides and/or fact checked the information included in this paper -

Dr Zoe Garrett, Senior Technical Adviser – Scientific Affairs, National Institute for Health and Care Excellence (NICE), United Kingdom

Jenna Dilkes, National Institute for Health and Care Excellence (NICE), United Kingdom

Gavin Kenny, National Institute for Health and Care Excellence (NICE), United Kingdom

Meindert Boysen, Head of International Affairs, National Institute for Health and Care Excellence (NICE), United Kingdom

Pauline McGuire, Principal Pharmacist, Scottish Medicines Consortium, Scotland

Dr Nicole Mittmann, Chief Scientist and Vice President, Scientific Evidence, Methodologies and Resources, and team at the Canadian Agency for Drugs and Technologies in Health (CADTH), Canada

Dr Alric Ruether, Head of International Affairs, and Irene Urbina of the Institute for Quality and Efficiency in Health Care (IQWiG), Germany

Dr Matthias Perleth, Head, Department of Medical Consultancy, The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA), Germany

Dr Miyoung Choi, Director of Clinical Evidence Research, National Evidence-based Healthcare Collaborating Agency (NECA), Korea

Dr Stephanie Vollenweider, Head Section Health Technology Assessment, Federal Department of Home Affairs, Federal Office of Public Health (FOPH), Switzerland

Lydia Loke, Lead Specialist, and team at Drug and Vaccine Evaluation, the Agency for Care Effectiveness (ACE), Singapore Ministry of Health, Singapore

The Department of Health and Aged Care project staff who coordinated the HTA Review and worked with AHTA on delivering each of the papers.

The HTA Policy and Methods Review Reference Committee for feedback and guidance throughout the project.

SCOPE OF RESEARCH

The research topics for Paper 1 are outlined in Research Topic section and summarised below.

The objective of Paper 1 was to compare the Australian HTA pathways and processes with international pathways and processes, and to identify similarities and differences between these jurisdictions. The characteristics of interest in these processes included mechanisms for prioritisation, transparency, involvement of stakeholders and alignment between registration and reimbursement processes.

The pathways and processes of interest related to the technologies described in the Review's terms of reference, which included specific reference to technologies: for rare diseases; for populations with high unmet clinical need; for disadvantaged populations; with uncertain long-term outcomes; that are co-dependent; that are high-cost; and, for which there is no application or sponsor.

SUMMARY OF FINDINGS

Literature searches identified 101 relevant peer-reviewed articles and 264 English language documents for inclusion in this scoping review.

HTA PATHWAYS

Twenty-seven international jurisdictions were reviewed, and most were found to have adopted a reactive HTA model, whereby HTA is conducted as a response to sponsors' (usually from industry) applying for medicine or technology reimbursement. Some jurisdictions conduct HTA proactively or through a hybrid model where the topic identified for an HTA is recommended by healthcare experts, patient advocacy organisations, and the government. In most of the jurisdictions using a proactive approach, horizon scanning is conducted to choose topics for the HTA. Irrespective of the model followed, for most jurisdictions the average time from submission of the evidence dossier by sponsors to the HTA funding recommendation is within the range of 17 – 32 weeks, with Japan reported to have the longest timeline of 60 – 72 weeks.

Although the HTA timeline follows a similar pattern across different jurisdictions, a large variation was observed in the timeline for patients to have *access* to funded medicines. Only the United Kingdom (UK) had a specific timeline for listing a medicine after an HTA funding recommendation is made. To reduce delays in patient access, we found that eight jurisdictions allow early access and prioritisation of certain medicines based on pre-determined criteria. This prioritisation mainly occurs through topic selection and expedited reviews for medicines that fulfil a high unmet clinical need. Countries such as France and Taiwan consider surrogate measures for health outcomes, as well as interim safety and clinical effectiveness results from clinical trials, to allow this early access.

Almost half (48%) of the jurisdictions reviewed aligned their regulatory and reimbursement process by allowing sponsors to submit the dossier for HTA assessment before market authorisation is granted. As formal data sharing often does not occur between HTA agencies and regulatory bodies in these jurisdictions, the HTA assessment and market regulation processes may only be aligned in terms of the timelines.

We observed that the evaluation of vaccines is frequently performed independent of the process used to assess medicines. In most key jurisdictions, the assessment of vaccines for provision and reimbursement is carried out by National Immunisation Technical Advisory Groups (NITAGs). A few countries, such as Australia, Netherlands, and France, have HTA agencies that conduct assessments of vaccines along with the NITAGs. The acceptability and implementation aspects of vaccination programs is frequently considered in vaccine assessments, in addition to the usual assessment of health benefits and patient-related factors. Canada is the only jurisdiction which reported utilising a framework for consideration of equity and access in their vaccine assessments. The academic literature indicated that assessments of vaccines often undervalue the importance

and societal benefits of vaccination programs and that these should be captured as part of the evaluation process.

Flexibility, transparency and access to medicines

In most jurisdictions, HTA outcomes are flexible with some medicines conditionally approved for reimbursement due to clinical need. Conditional approval includes utilisation of schemes like managed entry agreements (MEAs) – also known as managed access pathways (MAPs), and coverage with evidence development (CED) approaches. These schemes allow patients to access medicines that may not have received positive funding recommendations due to uncertainty inherent in the clinical evidence and/or the potential for considerable budget impact. More than half of the identified jurisdictions (67%) have method and process guidelines available on their website, which make it easy for sponsors and other stakeholders to identify the steps and nature of the assessment involved in the development and appraisal of HTA reports and dossiers. However, despite these predictable HTA assessment processes, it is not possible for sponsors to predict with certainty what price would result in a recommendation to fund a medicine or to what extent specific characteristics of the evidence influence whether a price is regarded as cost-effective by the decision-making body. We also identified that more than half of the jurisdictions (55%) allow sponsors to participate in the HTA process by inviting them to review, comment or attend committee meetings. The remaining jurisdictions do not provide any relevant information indicating the transparency of the process for sponsors. While most jurisdictions publish relevant documents regarding medicine funding decisions on their websites for the public to access, commercial or academic confidential information is frequently redacted. Recently, the National Institute for Health and Care Excellence (NICE), Institute for Clinical and Economic Review (ICER) and Canadian Agency for Drugs and Technologies in Health (CADTH) signed a joint transparency agreement indicating that they will not redact clinical data that are awaiting publication when they publish their respective funding decisions or recommendations.

Special Pathways

High-cost medicines and medicines addressing conditions with high unmet clinical need (such as rare diseases and antimicrobial resistance) provide significant challenges for jurisdictions. The challenges reported by different countries for listing these technologies through traditional HTA pathways are related, primarily, to uncertainties about clinical and cost-effectiveness and long-term effects. Most countries, including Australia, use managed access schemes (such as risk sharing arrangements or CED) to provide early access to these highly specialised technologies. There is also an increasing interest in real-world evidence of effectiveness (RWEE) to fill gaps in the evidence base for these technologies where it is not feasible to conduct randomised controlled trials. Agencies such as CADTH (Canada), NICE (UK), IQWiG (Germany), HAS (France), ZIN (the Netherlands), SMC (Scotland) and AIFA (Italy) consider supplementary real-world evidence to support reimbursement decisions for medicine resubmissions. Additionally, two countries (France, and the Netherland) exempt certain medicines from HTA, as added therapeutic value is already considered established i.e., for rare diseases and antimicrobials. Similarly, in Germany, orphan drugs are assessed through an abbreviated HTA process without the need to compare the medicine with an

appropriate comparator because added therapeutic value is always automatically assumed.

Equity and engagement

Most jurisdictions (22/27) reported that equity issues were considered in the HTA. These were mentioned either generally or in relation to a specific factor such as health status, age, and end-of-life care. Geographic or socio-economic factors were not typically considered as part of equity considerations (with the exception of the former being considered in Australia and Canada). Equity was typically regarded as a consideration that should be deliberatively considered by appraisal committees, given that HTA evaluation methods may not address how some population groups may be unfairly disadvantaged. Few programmatic or methodical approaches were reported that integrate equity considerations into assessment or appraisal. Equity seemed to be regarded as something in need of protecting (unjust inequalities should be reduced, or at least not introduced or compounded, when choosing whether to fund the technology) or as something for which the true value of a health technology might be assessed as higher (rarely lower) than indicated by the economic evaluation.

The stakeholder most consistently engaged in international HTA processes was industry (in multiple ways and at multiple timepoints) (23/27), then clinicians (22/27) and patients (21/27). In recent years HTA agencies seem to be increasingly active in the intensification of their engagement activities, especially with patients. Specialised technologies tend to lead to concerted efforts at stakeholder engagement. Invitations for public comment on assessment reports mostly occasion industry comments on the methods. Leading jurisdictions have dedicated patient engagement staff or committees, whose activities include conducting original qualitative research with patients, and they profess to use information from patients in all phases of the HTA pathway. However, problems with patient engagement were identified, including disagreement and uncertainty on their role and impact, and difficulties with recruitment, timing, and resources. Proposed solutions include acknowledging conflicts between epistemic traditions, reporting to patient groups how their inputs have been used (especially in appraisal decision making), and adequately resourcing proactive patient engagement.

IMPLICATIONS

The evidence obtained on different HTA pathways and processes indicates some variability in approach by different jurisdictions, which is not unexpected given the different health systems and methods of financing that operate internationally. There was no evidence obtained to indicate that one approach was more effective than another. HTA *'globalises the evidence'* but *'localises the decision'* and so each country has developed or adapted pathways and processes suitable for their local context, values and priorities.

A couple of areas of emerging consensus were noted. Many jurisdictions have introduced parallel regulatory/reimbursement processes to speed up access to medicines. For equity reasons they have also introduced funding access programs, such as MAPs and CED, to speed up access for patients with high unmet clinical need and where there are deficiencies in the available evidence base for the

technologies that treat them. There is also some agreement on the eligibility criteria for technologies to participate in these funding programs, although no two systems are completely alike.

The published evidence and stakeholder advice obtained on different HTA pathways and processes have been considered for their likely applicability to the HTA context in Australia. Equally, they have been assessed for their potential to achieve the objectives of the HTA Review to deliver a comprehensive set of recommendations for reforms to Government that:

1. are implementable and sustainable for both health funders (Commonwealth, state, and territory) and the health technology industry
2. deliver Australians equitable, timely, safe and affordable access to a high-quality and reliable supply of medicines for all Australians
3. adopt a person-centred approach in HTA
4. deliver the outcomes sought by recommendations from the Inquiry that are agreed in principle in the Government Response
5. further the objectives of the new National Medicines Policy
6. ensure HTA policy and methods are well adapted to, and capable of assessing, new technologies that are emerging or are expected to emerge in the coming years, and
7. do not compromise assessment of patient safety, effectiveness and cost, or advice to Government on subsidy of health technologies.

Bearing in mind these objectives, and considering the evidence obtained, three main areas of change were suggested – (1) optimising current approaches, (2) front loading, and (3) HTA pathway transformation.

Optimising current approaches

Pathway A was highlighted as a model approach for facilitating swift progress to a Pharmaceutical Benefits Scheme (PBS) listing after the Pharmaceutical Benefits Advisory Committee (PBAC) has recommended a medicine for funding. Part of the appeal of this pathway was the individual case management by the Australian Government Department of Health and Aged Care ('the Department'). If adopted more widely, this level of case management would require additional staff resourcing or re-deploying at Departmental level and might therefore be costly. However, Pathway A currently has an appropriate level of cost-recovery and if this case management approach was widened to all medicines undergoing re-submissions – or at least those medicines for which there is a high unmet clinical need - it could facilitate swifter PBS listings.

One of the other points mentioned in workshops was that PBAC Commentaries on applicant submissions could become more streamlined, such that they basically consist of an executive summary at the beginning and then the technical supporting information is provided in a series of attachments. Although this would reduce the review workload by the appraisal committees (i.e., PBAC and Economic SubCommittee, ESC, discussants) and the Department, the time taken to develop this document would likely be longer for evaluation groups, as producing a good synthesis takes time. However, if the evaluation period was extended slightly this approach might be achievable.

In addition, the reporting of the HTA assessment and appraisal process was often unclear to patients and other stakeholders due to a lack of tailored

communication. The current executive summary of PBAC Commentaries has multiple target audiences – it is meant to inform PBAC, the sponsor, and the public (as the executive summary of the Commentary forms the basis of the Public Summary Document). Ideally, to improve the transparency and coherence of communication, there would be one executive summary aimed at the PBAC and the sponsor with key points identified and justified but written in scientific language; and one Public Summary Document written in plain language and aimed at the public. The latter may be co-developed with patients. This approach would improve the transparency of the HTA process and support more effective patient engagement, particularly when combined with clearer guidance on the kind of information that patients can provide as a part of the assessment and appraisal process. Adequately resourcing patient engagement (e.g., with government funds and through the co-design of an enhanced consumer engagement process) stands as a potential means of improving patient engagement in the Australian HTA pathway.

Front loading

Mechanisms for monitoring emerging technologies and for determining the clinical place for medicines and technologies *before* they are submitted for funding (a 'proactive' approach) could facilitate swifter progress of a funding application through the HTA evaluation and appraisal process and allow greater stakeholder engagement.

An active horizon scanning process targeting 'disruptive' technologies (whether medicines, codependent technologies, or highly specialised therapies) could act as a feeder to HTA evaluations, either through the production of horizon scanning reports or 'proactive HTAs', to inform policy planning and funding decisions. International collaboration could help with this activity, but the aim would be to have a seamless integration with current HTA activity so that as new information emerges on 'disruptive' technologies an existing HTA report and economic model can be updated – as a *living HTA* process that provides an ongoing analysis to inform preparedness and policy decisions for selected technologies. Part of this horizon scanning and proactive HTA process could also involve identifying potential new patient indications for the 'repurposing' of medicines and technologies. This could trigger government negotiations with industry, patient groups and/or clinical professional societies to sponsor the proposed new indication.

In addition to proactive horizon scanning and integration of it with the HTA process, another element of front loading the HTA process could be to undertake a PICO[2] confirmation for first-in-class medicines/highly specialised technologies that have plausible significant added therapeutic value. These types of technologies are likely to be disruptive to the health system and yet little is often known of their place in clinical practice. Front loading a PICO process could reduce resubmissions that are rejected because of concerns with the population and comparator. See Paper 3 for further information.

[2] Population, Intervention, Comparator, Outcome

Transforming the current HTA pathway for medicines and technologies

Highly specialised technologies

It is apparent that some highly specialised technologies, including cell and gene therapies, have been progressed through the Medical Services Advisory Committee (MSAC) evaluation and appraisal pathway because they are technologies that would be administered in a public facility. Those that do not require administration in a public facility might meet the criteria for review by PBAC. While it might be more predictable and equitable for all highly specialised technologies to go through a single HTA pathway, it would also likely require amendments to be made to legislation concerning PBAC's remit or to the current (2020-2025) *National Health Reform Agreement* (NHRA). In the absence of these changes, at minimum a clear communication strategy could be employed so that there is transparency around the current process for selecting whether MSAC or PBAC reviews a particular highly specialised technology, and that the States and Territories are notified of this.

Introducing a model validation process

A consistent theme and source of frustration that emerged from stakeholder workshops was that the current PBAC HTA process has become a mechanism for price negotiation. This was described as industry providing multiple sequential submissions for evaluation to reduce decision uncertainty and arrive at a cost-effective price for the medicine. This "resubmission churn" can result in lengthy delays until a PBS listing is recommended by PBAC.

One possible alternative could be a 'model validation process' that would only be triggered if the medicine was considered to have added therapeutic value relative to the comparator, *and was provisionally PBS listed or funded on that basis*, but where there was decision uncertainty related to the economic model/price (see Figure 1). It would be an alternative to using PBAC decision-making as a mechanism for price negotiation. With this approach, the relevant ESC discussants, evaluators, Departmental staff and the sponsor would meet and work iteratively towards reducing uncertainty in the economic model assumptions and inputs in line with the advice from PBAC. This would occur essentially outside the 17-week assessment and appraisal cycle until such a point that a modified resubmission can be formally lodged and be reconsidered either by the full PBAC or the PBAC Executive. If the model uncertainties have been resolved and the remaining contributor to likely poor cost-effectiveness is simply the price, then there would be scope for direct negotiation between the sponsor and the Department on price before the model is resubmitted to PBAC for a decision (within a maximum of 12 months). If the model cannot be successfully validated and PBAC decides to reject the submission – even after the concentrated effort undertaken - then pricing policies and approaches to financial clawback for funding by the taxpayer would be triggered (and may include refunding and delisting of the medicine or the adoption of a fallback price), noting that the medicine was *provisionally* funded. There are three full PBAC meetings per year, so if three PBAC Executive meetings per year were also responsible for deciding whether the model had been validated or not, then listing decisions (whether

confirmatory or provisional) could be made every two months, rather than every four months as occurs currently.

Developing a Risk-calibrated Rapid Access HTA Pathway

There are many systems, like Australia, that have a formal HTA framework that examines the value of a health technology to society before it is funded by the taxpayer. A few countries have HTA pathways that subsidise technologies in anticipation of them being suitable for funding. That is, the technologies are subsidised either at market authorisation or post-market authorisation but prior to deliberation on cost-effectiveness or value for money.

The benefit of these anticipatory subsidisation processes is that patients can get swifter access to the technology, and potential health gains in terms of length and/or quality of life. This has flow on benefits to their carers, family members, the economy and society. Another benefit is that there is potentially more equitable access to technologies among specific population subgroups that are typically disadvantaged by current HTA processes.

For systems that subsidise technologies at market authorisation, but without – or with a delayed - HTA evaluation and appraisal (such as Germany), the risk is that a new treatment is funded that is not comparatively safe and is clinically ineffective or cost-ineffective when *compared* to standard medical management funded for that condition in the health system. Part of the reason for this is that the types of decisions made by regulators and HTA/payers differ. Regulators need to make a simple qualitative decision as to whether the clinical benefits outweigh the risks of the treatment to the individual. This contrasts with the HTA agency or payer perspective which is about making a quantitative decision on the *magnitude* of clinical benefit *or added therapeutic value* over existing treatments at the population level (see Section 6.3.4). Thus, the HTA/payer perspective is about whether there is sufficient value demonstrated by the outcomes reported in the evidence dossier to spend taxpayer funds on the treatment in question, as opposed to spending it on other areas of the health system that are equally in need. The HTA/payer perspective considers the opportunity cost of the treatment. If too many medicines are funded at market entry that are not-cost-effective it means - even if the price is later re-set - that those funds cannot be spent on other areas of the health system, potentially threatening the system's sustainability.

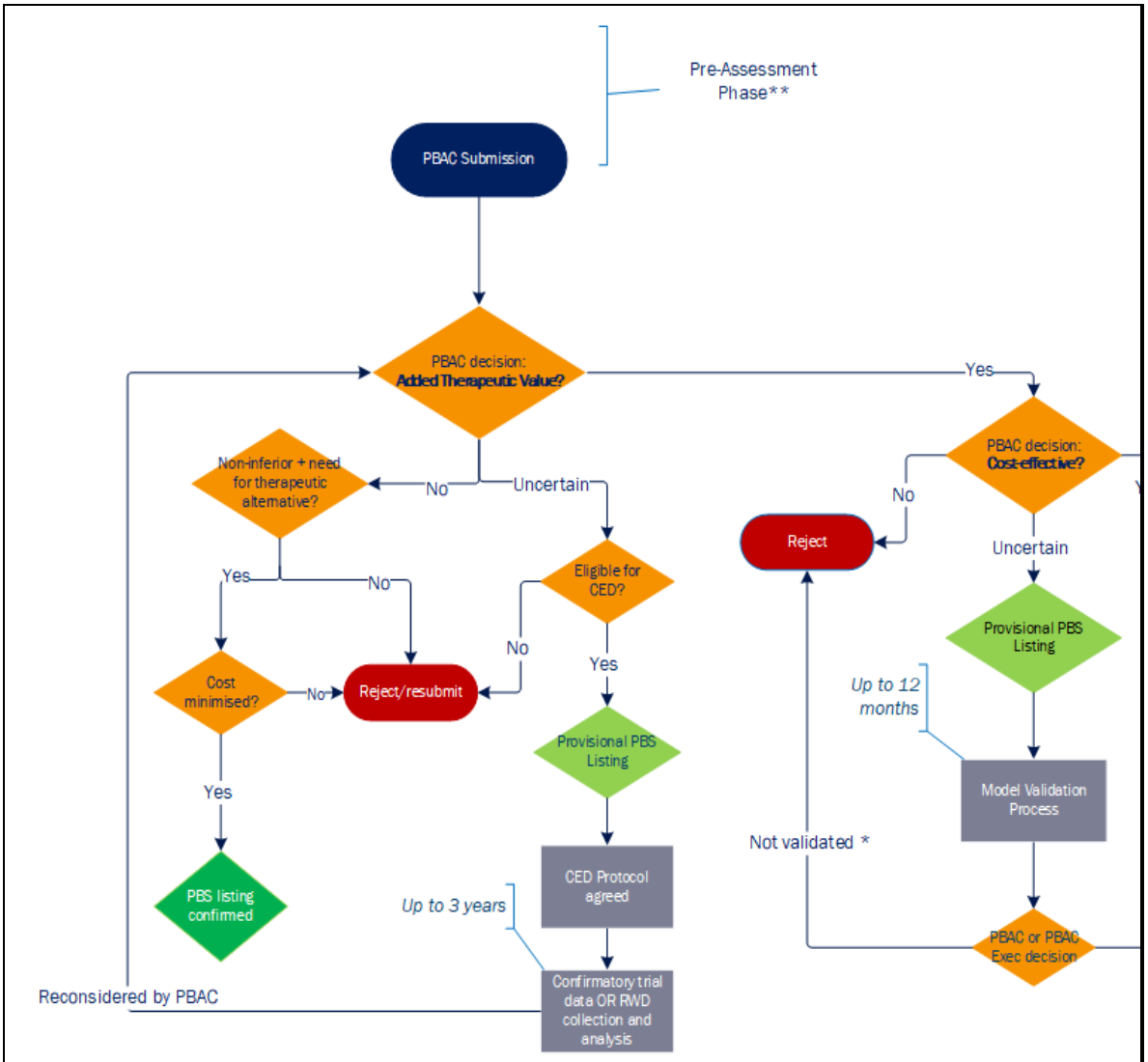
One mechanism for providing funded access to medicines at market authorisation, while retaining an HTA perspective on the technology, is to institute 'parallel regulatory/HTA processing'. Australia is a leading exponent of this approach, with PBAC typically making its initial funding decision (at least for cancer medicines) 17 weeks prior to listing of medicines on the Australian Register of Therapeutic Goods. The problem is that nearly two-thirds of PBAC decisions concerning the initial submission are negative. Uncertain cost-effectiveness is one of the main reasons - and so a cycle of resubmissions commences, delaying patient access to the medicines. However, it is noted that most of those medicines considered to have added therapeutic value, or that are non-inferior, are eventually subsidised.

There are systems that fund technologies at market authorisation or post-market authorisation because they show promise of addressing unmet clinical need for rare diseases or severe/life threatening disease, but for which the evidence base is immature or never likely to eventuate. As has been demonstrated by several international HTA systems, CED in some form is likely to be beneficial if applied to

priority disease areas where there is high unmet clinical need, where the technology shows promise but there is limited evidence available, and where the added therapeutic value and cost-effectiveness are uncertain. A clear definition of high unmet clinical need and a process that targets treatments in high priority disease areas would be crucial to the success of any such program and would need to be developed by the Department, in consultation with stakeholders. Additionally, there would need to be clear expectations around the development of evidence to confirm (or not) the promise of the treatment.

One possible approach to balancing the benefits of rapid access to health technologies with safeguards for patients and the economic viability of the health system, is to create an HTA pathway that triages the assessment and appraisal approach according to the risk (Figure 1). Such a pathway should be flexible enough to change the time point for a PBAC funding decision, depending on the level of decision uncertainty, and thus the associated risk of an incorrect decision. It should, however, retain a large element of its predictability by having defined timings for submission, assessment and appraisal. Such a pathway is proposed below. It builds on the existing PBAC HTA pathway but incorporates a provisional listing component, a model validation component and a CED component. These could be separated out and applied singly, or altogether, or could be introduced in a staged manner.

For medicines undergoing the parallel process that is currently undertaken between TGA and PBAC, the introduction of this HTA Pathway would essentially mean that medicines are *PBS listed at market entry* if found to be of added therapeutic value or eligible for CED by the PBAC. Medicines undergoing a sequential (regulation followed by HTA) process would also be funded earlier than currently. The proposed model validation process would reduce 'resubmission churn' and speed up the time to PBS listing and patient access to medicines. Orphan drugs for rare diseases with a scant evidence base could be funded while data on performance are obtained in an ongoing fashion. As in the current process, non-inferior medicines would be cost-minimised against a comparator and PBS listed to ensure the supply of therapeutic alternatives in the event of medicine shortages.



* Activate clawback provision on provisional listing. Possibly used to fund Horizon Scanning and proactive HTA, given cost-recovery for submission process is already built-in to the existing PBAC submission process.

** Could include PICO scoping phase for first-in-class, potentially disruptive, medicines and technologies.

Added therapeutic value is defined as a significant[1] improvement in population health outcomes obtained with a new medicine or technology when compared to the best available therapeutic alternatives.

[1] 'Significant' means a clinically important improvement in health outcomes. It is not demonstrated solely by a statistically significant difference in health outcomes.

Figure 1 Risk-calibrated Rapid Access HTA Pathway for PBAC submissions

The Risk-calibrated Rapid Access Pathway picks up elements of some of the swifter evaluation and appraisal pathways used overseas but adapts these to the unique Australian context. The Pathway is patient-centric, equitable, transparent, balances speed with rigour and aims to keep the Australian health system sustainable.

LITERATURE SEARCH RESULTS

The process of selecting relevant documents from grey literature (reports, guidelines and webpages of HTA agencies and governments) and peer-reviewed journal articles for this scoping review is given in the PRISMA-ScR flowchart (Figure 34).

Searches identified 101 relevant peer-reviewed articles and 264 English language documents for inclusion in this scoping review.

The documentation for many non-English speaking countries was not available in English, therefore, where possible, information was extracted from peer-reviewed journal articles. Many publications identified from bibliographic databases were cross-jurisdictional comparisons of HTA processes and pathways on topics such as timelines or early access. Patient engagement processes were predominantly addressed in the peer-reviewed literature.

For some concepts where this was no standardised definition used across jurisdictions. It was therefore unclear whether similar interpretations of the concept were being reported. These concepts included the number of steps involved in HTA pathways, predictability, flexibility and transparency.

HEALTH SYSTEM CHARACTERISTICS

With respect to health system characteristics, the following items were considered:

- What is the health system financing model? Categorised as:
    - Direct (out-of-pocket) purchase where patients pay for healthcare services directly from their own money,
    - Third-party single-payer system: A single entity (such as the government) pays for all healthcare services, and
    - Pooled, multi-payer system where multiple entities (such as government/social insurance organisations or private insurance companies) pay for healthcare services.
- Who pay/s for different technologies: national government, regional government, employer, citizen (self-funded)
- Kind of HTA system
    - Agency involved in assessment,
    - Agency involved in appraisal, and
    - Model of conducting HTA: proactive, reactive or hybrid.

These concepts and the associated categorisations are given in Table 2.

Table 2 Health System Characteristics

Jurisdiction		Health care financing and Health care delivery		HTA system		
		What is the health care financing model?	**Who is/are the payer/s for medicines, vaccines, and codependent tests?**	**Who conducts the assessments?**	**Who conducts the appraisal?**	**Is HTA undertaken proactively, reactively, or both?**
Australia		Pooled, multi-payer system Universal health insurance scheme: Medicare	National government for out-patient costs, state/territory governments for in-patient costs (public system), private health insurers (private system) plus a portion of out-of-pocket costs by patients who do not meet safety net threshold.	External HTA agencies: Universities/academia	Pharmaceutical Benefits Advisory Committee (PBAC) for medicines (different appraisal body for medical technologies)	Reactive
Austria		Pooled, multi-payer system Universal health insurance scheme: Statutory health insurance	Statutory health insurance (SHI), consisting of non-competing, not-for-profit, nongovernmental health insurance plans; and private health insurance (Voluntary health insurance)	In-house government HTA unit: Dachverband der Sozialversicherungsträger (HVB) AND External HTA agencies: Universities/academia (but mostly for medical technologies)	HVB	Reactive
Belgium		Pooled, multi-payer system Universal health insurance scheme: Sickness fund	Compulsory health insurance (99% population), and public centre for social assistance (1% of population).	In-house government HTA unit: National Institute for Health and Disability Insurance (NIHDI) AND Independent HTA agency with relationship to government: The Belgian Healthcare Knowledge Centre (KCE)	NIHDI	Reactive
Canada	CADTH (national HTA agency)	Pooled, multi-payer system Universal health insurance scheme: Canadian Medicare	Mostly provincial and territorial (P/T) governments. And a national insurance program for prescription drugs (Pharmacare) for expansion of public funding and coverage is in progress.	Independent HTA agency with relationship to government: Canadian Agency for Drugs and Technologies in Health (CADTH)	Common Drug review (CDR): Canadian Drug Expert Committee (CDEC) Oncology drugs: Pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC)	Hybrid

Jurisdiction		Health care financing and Health care delivery		HTA system		
		What is the health care financing model?	**Who is/are the payer/s for medicines, vaccines, and codependent tests?**	**Who conducts the assessments?**	**Who conducts the appraisal?**	**Is HTA undertaken proactively, reactively, or both?**
	INESSS (Quebec)		Drug Insurance Plan and other government sponsored supplementary health benefits programs.	Independent HTA agencies with relationship to government: Scientific staffs from Institut national d'excellence en santé et services sociaux (INESSS), and members of the Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription (CSEMI).	CSEMI, and Board of Directors of INESSS or Comité de l'évolution des pratiques en oncologie (CEPO) for oncology medicines.	Reactive
	Ontario (HQ)		Ontario Public Drug Programs and other government sponsored supplementary health benefits programs.	Participant in the national Common Drug Review, managed by CADTH	CADTH	Hybrid
	IHE (Alberta)		Alberta Health Care Insurance Plan (AHCIP), and other government sponsored supplementary health benefits programs	Participant in the national Common Drug Review, managed by CADTH	CADTH, and Alberta's Expert Committee on Drug Evaluation and Therapeutics (ECDET)	Hybrid
Denmark		Third-party single payer system Universal health insurance scheme	National government (through regional governments)	In-house government HTA unit: Danish Medicines Agency (DMA)	DMA	Reactive
Finland		Third-party single payer system	National government (through regional government)	In-house government HTA unit: The Pharmaceutical Pricing Board (HILA)	HILA	Reactive
France		Pooled, multi-payer system Universal Health insurance scheme: Statutory health insurance (SHI)	Statutory health insurance (SHI) plans, paid through tax arrangements, and a small amount from state subsidies.	Independent HTA agency with relationship to government: The Haute Autorité de santé (HAS)	HAS	Reactive
Germany		Pooled, multi-payer system	Statutory health insurance (SHI), consisting of competing, not-for-profit, nongovernmental health insurance plans known as sickness funds; and private health insurance	Independent HTA agency with relationship to government: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; (IQWiG)	Gemeinsamer Bundesausschuss (G-BA)	Reactive
Ireland		Pooled, multi-payer system	National government and Citizen (self-funded)	Independent HTA agency with relationship to government:	Health Service Executive (HSE) Drugs Group	Reactive

Jurisdiction	Health care financing and Health care delivery		HTA system		
	What is the health care financing model?	**Who is/are the payer/s for medicines, vaccines, and codependent tests?**	**Who conducts the assessments?**	**Who conducts the appraisal?**	**Is HTA undertaken proactively, reactively, or both?**
			National Centre for Pharmacoeconomics (NCPE), and Health Information and Quality Authority (HIQA)		
Italy	Third-party single-payer system Universal health insurance scheme: National Health Service (*Servizio sanitario nazionale,* or SSN)	National government	In-house government HTA units: *At national level:* Italian Medicine Agency – AFIA HTA and Pharmaceutical Economy Division (HTA-PED) *At regional level:* Emilia-Romagna Regional Health Authority (RER) and Veneto	*At national level:* AIFA Scientific Technical Committee (CTS) and Pricing and Reimbursement Committee (CPR)	Reactive
Japan	Pooled, multi-payer system Universal health insurance scheme: Statutory insurance and public social assistance program	Statutory health insurance (SHI) (covers 98.3% population), and public social assistance program (covers 1.7% population). Also >70% of population utilise supplementary private coverage.	External HTA agencies: Independent specialist organisations	Central Social Insurance Medical Council (CSIMC)	Proactive
Norway	Third-party single-payer system Universal health insurance scheme: National Insurance Scheme (NIS), or *Folketrygd*	National government	In-house government HTA unit: *For STAs:* Norwegian Medicines Agency (NoMA) For MTAs or full HTA: The Norwegian Institute of Public Health (NIPH)	Decision forum –Norwegian Directorate of Health	Reactive
Poland	Third-party single-payer system Universal health insurance scheme: Social health insurance	Social Health Insurance – National Health fund (NFZ)	Independent HTA agency with relationship to government: Agency For Health Technology Assessment and Tariff system (AOTMiT)	Transparency Council	Reactive

Jurisdiction	Health care financing and Health care delivery		HTA system		
	What is the health care financing model?	**Who is/are the payer/s for medicines, vaccines, and codependent tests?**	**Who conducts the assessments?**	**Who conducts the appraisal?**	**Is HTA undertaken proactively, reactively, or both?**
Singapore	Pooled, multi-payer system Universal health insurance scheme: MediShield Life	Government subsidies, MediShield Life (universal basic health scheme), MediSave (national medical saving scheme, helping out-of-pocket costs), and Medifund (government safety net for patients in need).	In-house government HTA unit: The Agency for Care Effectiveness (ACE)	MOH Drug Advisory Committee (DAC)	Hybrid
South Korea	Pooled, multi-payer system Universal health insurance scheme: National health insurance and medical aid program	The national health insurance (NHI)(covers 97% of population), and medical aid program (only for low-income groups, cover 3% population).	Independent HTA agency with relationship to government: Health Insurance Review and Assessment Service (HIRA) for medicines (different assessment and appraisal bodies for medical technologies)	Pharmaceutical Benefit Coverage Assessment Committee (PBCAC)	Hybrid
Spain	Third-party single-payer system Universal health insurance scheme: National Health System (Sistema Nacional de Salud; SNS)	National Health System (NHS)	In-house government HTA units: At national level, as well as regional HTA agencies	Ministry of Health–MSCBS	Reactive
Sweden	Third-party single-payer system Universal health insurance scheme: National Health Insurance	National Insurance	In-house government HTA units: Tandvårdsoch Läke-medelsförmånsverket (TLV), and Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)	The Pharmaceutical Benefits Board	Reactive
Switzerland	Pooled, multi-payer system Universal health insurance scheme	Compulsory/ mandatory health insurance is delivered by different insurers	In-house government HTA units: Health Insurance Benefit Division (EAE review) AND External HTA agencies: External HTA partners (Federal HTA programme)	Federal Commissions & Federal Office of Public Health	Reactive

Jurisdiction		Health care financing and Health care delivery		HTA system		
		What is the health care financing model?	**Who is/are the payer/s for medicines, vaccines, and codependent tests?**	**Who conducts the assessments?**	**Who conducts the appraisal?**	**Is HTA undertaken proactively, reactively, or both?**
Taiwan, Republic of China		Third-party single-payer system Universal health insurance scheme: National Health Insurance (NHI)	National Health Insurance (NHI)	Independent HTA agency with relationship to government: Center for Drug Evaluation (CDE)	National Health Insurance Administration (NIHA) & Pharmaceutical Benefit and Reimbursement Scheme (PBRS)	Reactive
The Netherlands		Pooled, multi-payer system Universal health insurance: statutory health insurance from private insurers	Public and private insurance with public insurance through premiums, tax revenues, and government grants.	Independent HTA agency with relationship to government: Zorginstituut Nederland (ZIN)	Advies Commissie Pakket (ACP)	Hybrid
United Kingdom	England	Third-party single-payer system (National Health Service NHS) Universal health insurance: National Health Service NHS	National Government	Independent HTA agency with relationship to government: National Institute for Health and Care Excellence (NICE)	Independent advisory Committee (consisting of members external to NICE)	Proactive
	Wales		National Government	Independent HTA agencies with relationship to government: The National Institute for Health and Care Excellence (*NICE) advice available:* Follow NICE advice If NICE advice not available: All Wales Medicines Strategy Group (AWMSG)	NICE advice available: The National Institute for Health and Care Excellence (NICE) NICE advice not available: All Wales Medicines Strategy Group (AWMSG)	Proactive
	Scotland		National Government	Independent HTA body with relationship to government: Scottish Medicines Consortium (SMC) (New Drug Committee)	Scottish Medicines Consortium (SMC)	Reactive

Jurisdiction		Health care financing and Health care delivery		HTA system		
		What is the health care financing model?	**Who is/are the payer/s for medicines, vaccines, and codependent tests?**	**Who conducts the assessments?**	**Who conducts the appraisal?**	**Is HTA undertaken proactively, reactively, or both?**
US		Pooled, multi-payer system	Combination of national and state governments (Medicare and Medicaid) and private insurance by employers and citizens (self-funded)	External HTA agencies: Different payers and independent HTA agencies (e.g., Institute for Clinical and Economic Review, ICER) (Different assessment and appraisal bodies for medical technologies)	Individual payers	Proactive (ICER) Reactive (Agency for Healthcare Research and Quality (AHRQ) for medical technologies)

Reference: https://qdd.oecd.org/subject.aspx?Subject=hsc (OECD health system survey)

CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; MTA= Multiple Technology Assessment; MoH= Ministry of Health; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; STA= Single Technology Assessment; ZIN = Zorginstituut Nederland (National Health Care Institute)

HEALTHCARE FINANCING AND DELIVERY

In the analysed jurisdictions, there were 16 jurisdictions with pooled, multi-payer healthcare systems, where multiple entities (such as government/social insurance organisations or private insurance companies) pay for healthcare services. Eleven jurisdictions have single payer systems, where a single entity (such as the government) pays for all healthcare services for their citizens. A brief description of each of the key jurisdictions is provided below, with further details on all jurisdictions to be found in Supplementary Data to this report (Attachment 1).

Australia

The Australian health care system consists of multiple payers. Responsibility for health care primarily falls to both the Australian Government and State/Territory Governments. The Australian Government and State/Territory Governments are responsible for funding public hospitals, although the State/Territory Governments are responsible for managing them and therefore purchase medicines and technologies that are used for inpatients. Public hospitals are funded through activity-based schemes. The Australian Government provides funding for outpatient services and rebates private health care. Private health insurers pay for hospital services as a private patient and for non-medical health services. Funding of services is generally provided on a fee-for-service basis. Medicines that are not provided in a hospital setting that are on the Pharmaceutical Benefits Scheme (PBS) are funded by the Australian Government, with a minority of the funding derived from patient co-payments. Medicines that are not included on the PBS (but are approved by the TGA) can be purchased at full cost by the patient.

HTA System

The Australian HTA process for medicines contains a few key steps. These include receipt of an application / submission from an industry sponsor; evaluation of the submission; sponsor response to the evaluation; Economic Subcommittee (ESC) consideration; sponsor response to the subcommittee summary document; and appraisal and a recommendation by the PBAC. If recommended, a medicine can be approved by the Minister for Health and Aged Care (or a delegate), or by Cabinet (if >$20 million). There are three 17-week evaluation and appraisal PBAC cycles (from submission to PBAC consideration). Major submissions are evaluated by external independent/academic HTA groups during the first 8.5 weeks [10] (see Figure 2). Steps between PBAC recommendation and listing on the PBS may include negotiations of price, risk share arrangements or other conditions, and are typically not transparent due to the commercially sensitive nature of the discussions.

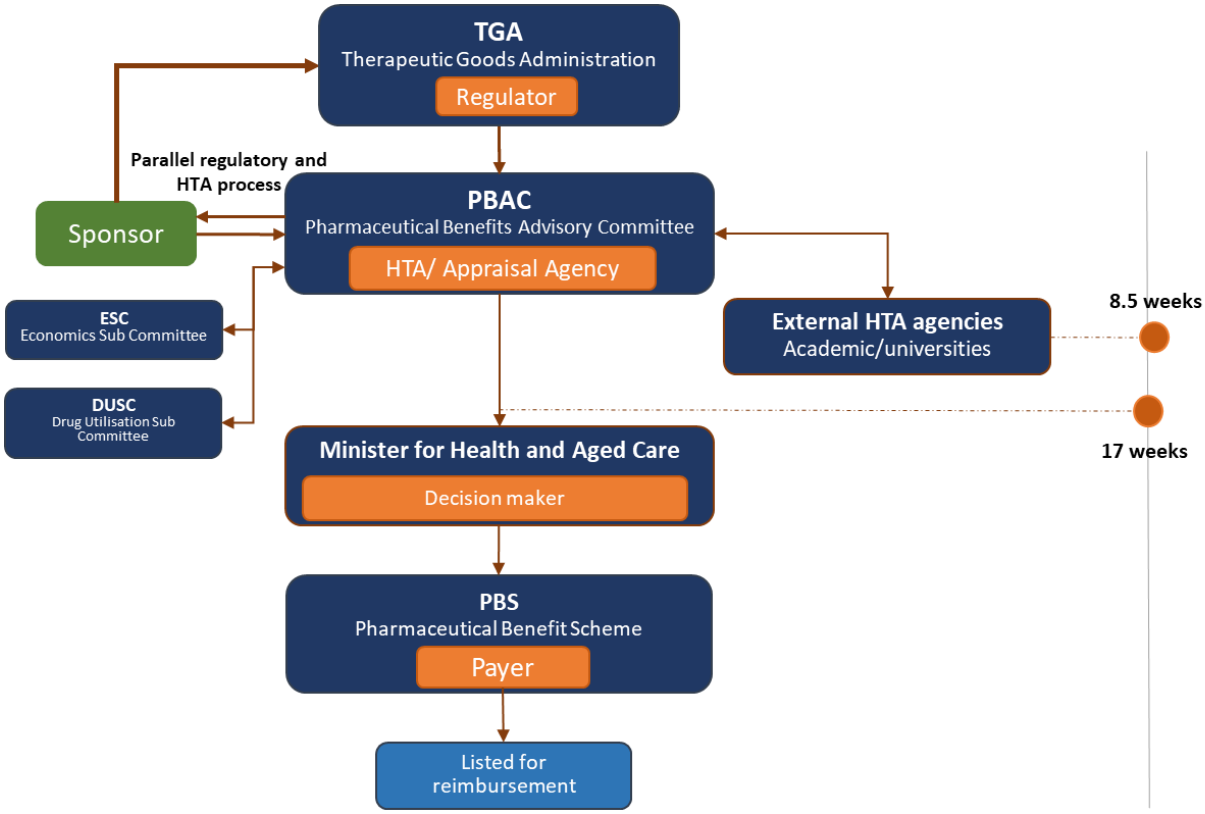


Figure 2 Flowchart for HTA Process in Australia

COUNTRIES WITH POOLED MULTI-PAYER HEALTH SYSTEMS

Canada

The Canadian health system is decentralised and provides universal, publicly funded healthcare. The system is administered primarily by the country's 13 provinces and territories. Each province or territory has its own insurance plan, and each receives cash assistance from the federal government on a per-capita basis. The provincial and territorial governments have most of the responsibility for delivering health and other social services. The federal government is also responsible for some funding and/or delivery of primary and supplementary services for certain groups of people (i.e., First Nations people living on reserves; Inuit; serving members of the Canadian Armed Forces; eligible veterans; inmates in federal penitentiaries; and some groups of refugee claimants). Each province provides its own insurance plan to residents; however, the federal government provides funding assistance on a per-capita basis.

The provinces and territories' insurance plan mostly covers physician and hospital related services on a prepaid basis, whereas services not covered by Canadian Medicare are paid through employer-based and private insurance plans, alongside out-of-pocket payments. There is a structured statutory benefit package, meaning that coverage can vary across insurance plans at province and territory level for services such as

outpatient prescription drugs, dental care, vision care, mental health care, medical devices, and midwifery services [11].

Despite the health system offering universal health care, there is no universal coverage for prescription medicines. The fragmented landscape of drug insurance plans leaves many Canadians without adequate coverage to afford their medicines. There are many government-run and private medicine benefit plans; however, these plans usually have annual or lifetime limits on coverage. Therefore, many people have to pay part of the cost as out-of-pocket payments and deductibles. In 2018, the House of Commons Standing Committee on Health recommended establishing a single-payer, universal, public national Pharmacare program by expanding the *Canada Health Act* to include prescription drugs as an insured service. The Private Member's Bill was introduced in 2020 and was rejected by Parliament [11, 12].

HTA System

The Canadian Agency for Drugs and Technologies in Health (CADTH) provides independent, nonbinding information and advice for the country's publicly funded health care systems (except for Quebec). CADTH oversees two pan-Canadian HTA processes in Canada: the pan-Canadian Oncology Drug Review (pCODR) and the Common Drug Review (CDR) (Figure 3). The pCODR primarily focuses on evaluating oncology medicines, whereas the CDR focuses on all other types of medicines. Each program has separate independent expert committees that provide reimbursement recommendations. For the CDR, these recommendations are directed to federal, provincial, and territorial drug plans, excluding Quebec. As for pCODR, in addition to federal, provincial, and territorial drug plans, provincial cancer agencies also receive the recommendations.

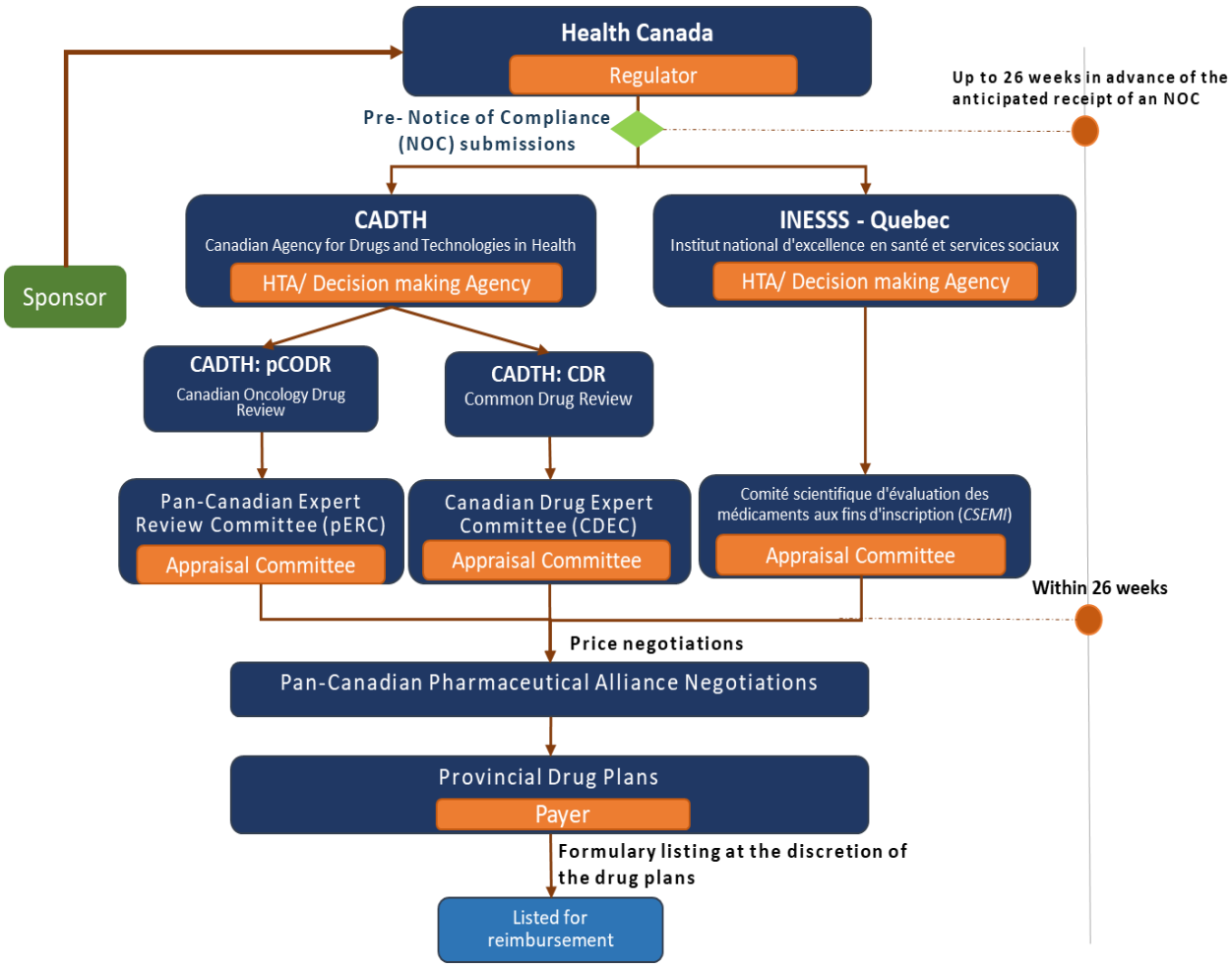


Figure 3 Flowchart of HTA process in Canada

France

France has a multi-payer healthcare system, with universal coverage provided through statutory health insurance (SHI) [13]. There are two main players: SHI and the national government. Despite recent decentralisation of power to regional health agencies, the national government still has majority governance of health services. SHI is financed by payroll tax, income tax, tax levies (from tobacco, alcohol, pharmaceuticals companies, private health companies) and state subsidies [13]. Most of the hospitals and physician-based services, long-term care and outpatient prescription medicines are covered through SHI. However, patients are responsible for copayments and coinsurance for physician charges exceeding the covered fees. 95% of the population have private supplementary insurance to cover copayments and other services such as dental, vision and hearing care.

In total 83% of the health expenditure is financed by SHI whereas out-of-pocket payments and private insurance finance the remaining 17%.

HTA System

The Haute Autorité de santé (HAS) is the independent centralised national HTA body responsible for conducting the assessment of medicines in France. It comprises of eight committees with distinctive functions [14]. For instance, the transparency committee (TC) assesses and makes recommendations for medical products, whereas the Economic and Public Health Committee (CEESP) undertakes the economic assessment [15] (see Figure 4).

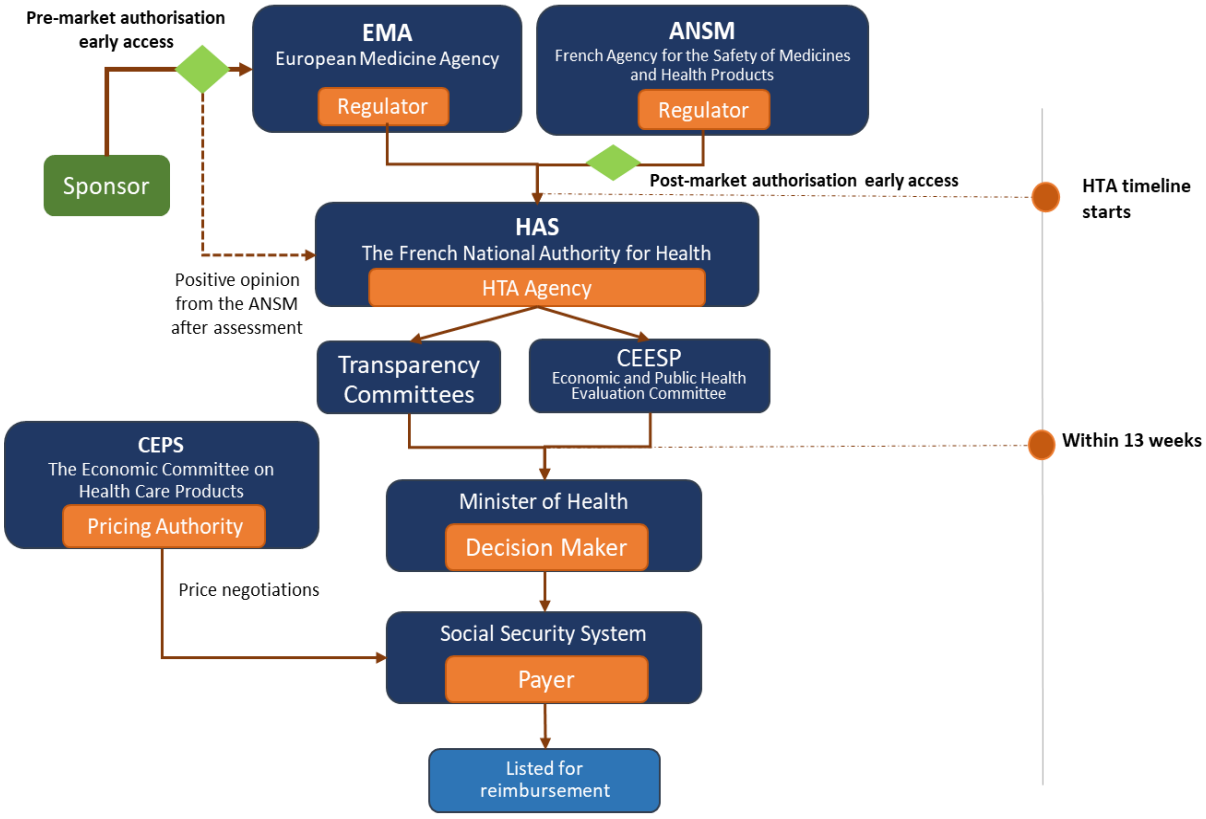


Figure 4 Flowchart of HTA process in France

Germany

Health insurance is mandatory in Germany and is provided by two subsystems: statutory health insurance (SHI) comprising of nongovernmental, non-for-profit health insurance plans known as sickness funds; and private health insurance. Almost 88.1% of the population is enrolled in the SHI which provides coverage for inpatient, outpatient, prescription drugs and mental health services. Both employers and workers contribute to the sickness funds through wage contributions (14.6%) and a supplementary contribution (1.6% of wage). Citizens with annual salary more than the wage threshold (EUR 66,600) can opt out of SHI and select a private health insurer, but the government provides no subsidy for private insurance. The national government is not directly involved in the delivery of the healthcare services but has wide-ranging regulatory authority. Under the statutory supervision of the Federal Ministry of Health, the Federal Joint Committee (G-BA) determines which services can be covered by sickness funds. The Federal Joint Committee (G-BA) is a public legal entity comprising of four umbrella

organisations: the National Associations of Statutory Health Insurance Physicians and Dentists, the German Hospital Federation, and the Central Federal Association of Health Insurance Funds.

HTA System

An independent scientific institute, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) is responsible for evaluating the added therapeutic value of medicines, non-drug therapeutics, diagnostic and screening technologies [13]. The IQWiG is commissioned by G-BA to assess medicines, except for orphan drugs which are assessed in-house by the G-BA.

Patients can have funded access to medicines following market authorisation. For the first six months, the company can set the price of the medicine during which the medicine is assessed through an HTA process to determine if it provides additional therapeutic value and whether the price will be covered by SHI funds. When the conclusion is that there is no added therapeutic value, the medicine is added to a reference price group. If added therapeutic value is demonstrated, a price amendment is negotiated between the SHI funds and the medicine sponsor (Figure 5).

The sponsor needs to submit a detailed dossier to the Federal Joint Committee (G-BA) within three months of first marketing in Germany. The G-BA transfers the submitted dossier to IQWiG for a detailed comparison of the new drug with the established drug (the comparator). The G-BA assesses the IQWiG recommendation, additional evidence submitted by the pharmaceutical company and makes the final decision on the additional therapeutic value of the medicine. See section 0 for more information on how added therapeutic value is determined (page 79). Generally, no cost-effectiveness analyses are performed by IQWiG. However, if sponsors and SHI bodies cannot reach an agreement on coverage during price negotiations, health economic parameters may be used to reach an agreement.

A new law, the Gesetzliche Krankenversicherung Financial Stabilization Act (GKV-FinStG), came into effect in November 2022 to reduce pharmaceutical expenditures. The following changes were introduced in this law that impact the medicine approval process:

I. Reduction in free pricing period

The initial 12 months' free pricing period, in which manufacturers are free to set the price of their product, was reduced to six months. The negotiated prices are published approximately one year after the product launch, as per standard negotiation timelines. This implies that the sponsors may need to pay back some of the revenue earned after six months to the sickness funds if there is a difference in the negotiated reimbursement price and freely set price by the sponsor.

II. New Pricing guardrails

Under the new law, new pricing rules can impact the price of the medicine depending on the G-BA added benefit ruling, in case the most economical appropriate comparator therapy (ACT) is still under patent protection. The new pricing regulation in the context of a patent-protected ACT are:

- If a medicine has no added therapeutic value, the price should reflect at least 10% discount.
- If a medicine is identified to have nonquantifiable or minor added therapeutic value, the price cannot exceed the ACT costs. Previously, added therapeutic value that was minor or nonquantifiable still led to negotiations for price premium over ACT.
- If a medicine has a considerable or major added therapeutic value, less restrictive pricing guardrails apply.

An additional regulation is applied for in circumstances where the reference price benchmarks are under patent protection but have not been subjected to price negotiations. The reference price for these benchmarks need to be calculated with a theoretical 15% discount and are not based on their actual price.

III. Volume-based Pricing Model

Previously, the budget or volume considerations were optional in the price agreements between sponsors and Germany's umbrella payer GKV-Spitzenverband (GKV-SV). However, under the new regulation, the price-volume agreements and/or budget caps are deemed mandatory.

IV. Rebates

In this new law a 20% rebate was introduced for combination treatments that were first launched after 2011 and have explicit market authorisation for combination use. Combination treatments with considerable and major added therapeutic value are exempted from this rebate. The G-BA in currently working on the guidelines for the operationalisation and classification of this rebate. There is also a temporary increase in the mandatory rebate for the sponsors from 7% to 12% until December 2023 [16].

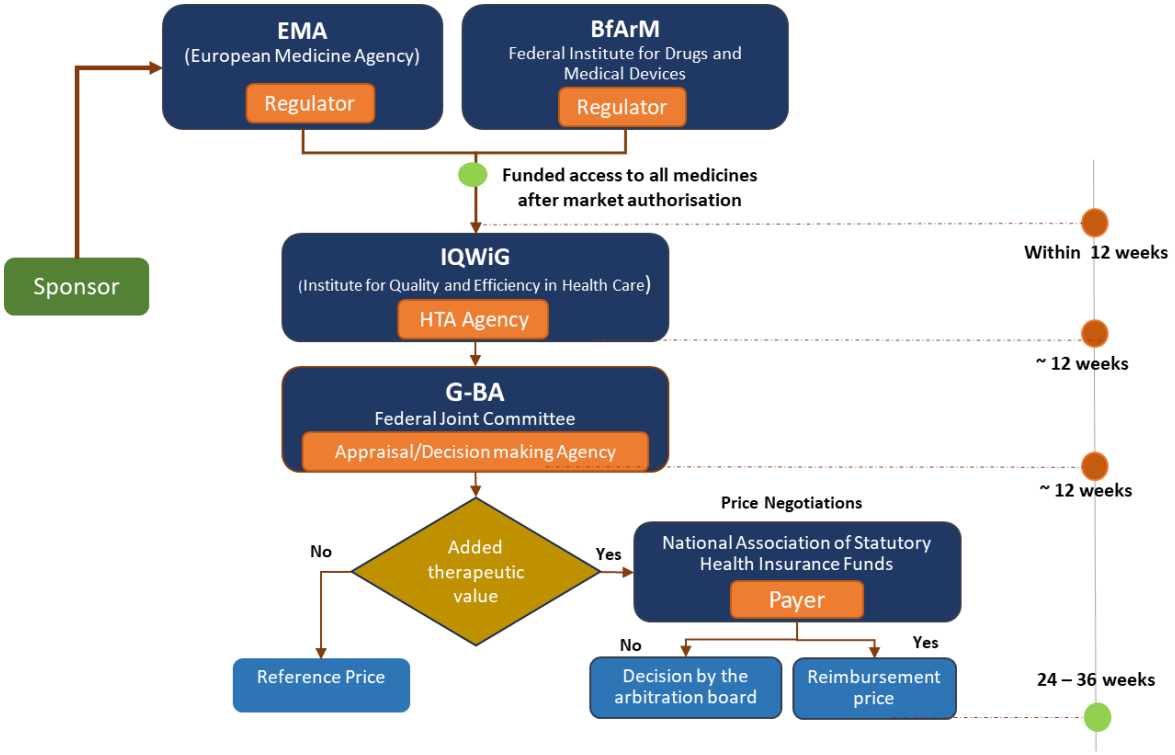


Figure 5 Flowchart of HTA process in Germany

South Korea

The healthcare insurance in South Korea (subsequently referred to as Korea) consist of: National Health Insurance (NHI) and Medical Aid. Most of the population is covered by the NHI, while the low-income population is covered by the Medical Aid [17]. The NHI is predominantly funded by premium paid by the potential beneficiaries (being paid by both employers and individuals) and government subsidies [18]. The NHI provides a benefit package for different services such as emergency care, diagnosis, treatment, pharmaceutical, traditional medical care, and dental care. Patient co-payments range from 30% - 60% for outpatient services, whereas hospital care is subjected to 20% co-payments. Due to the high co-payment associated with the NHI, 90% of the population also have a private health insurance plan. Medical Aid, on the other hand, is a government subsidy program to aid those with a low-income population for healthcare services. It covers both insurance premiums as well as co-payments.

HTA System

The National Evidence-based Healthcare Collaborating Agency (NECA) is a representative HTA agency in Korea, but only conducts assessments of medical services provided under the Medical Act. HTA for medicines are conducted by the Health Insurance Review and Assessment Service (HIRA) [19]. The Assessment Committee within HIRA develops the HTA report in terms of evaluating the comparative effectiveness and cost-effectiveness of the medicine[20]. The Pharmaceutical Benefit Coverage Assessment

Committee (PBCAC) conducts the HTA appraisal and makes the funding recommendations [20] (see Figure 6).

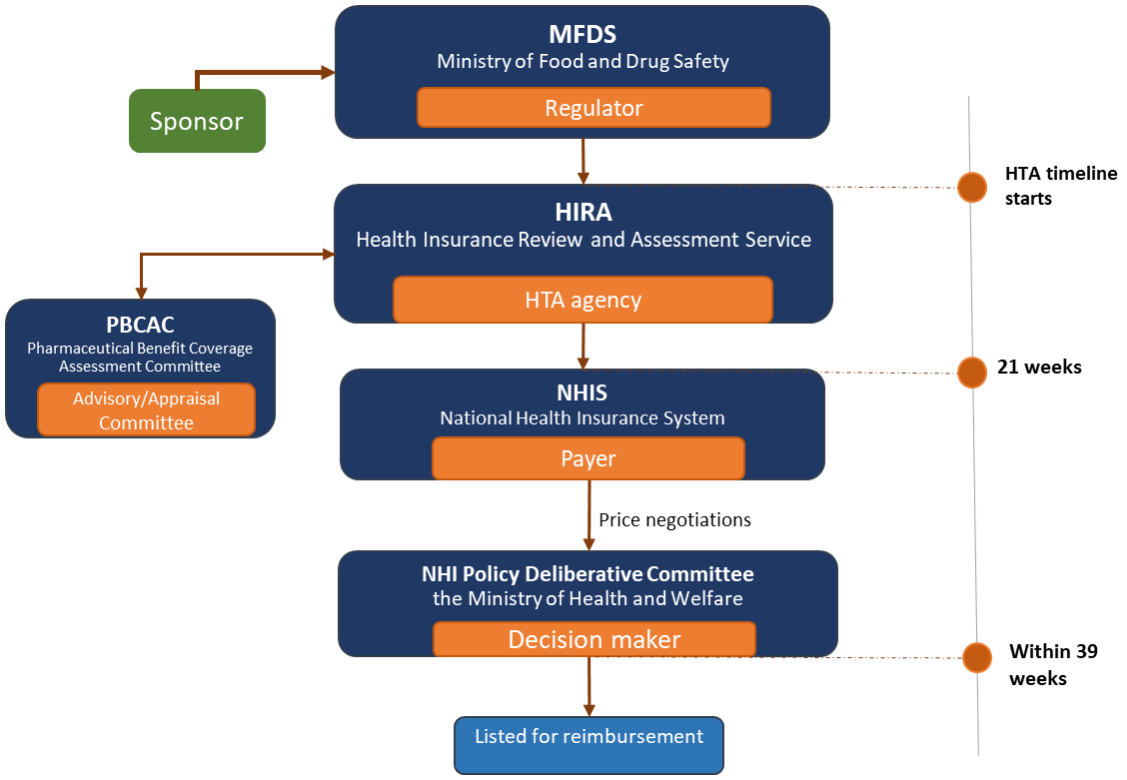


Figure 6 Flowchart of HTA Process in South Korea

The Netherlands

The Dutch healthcare financing model is based on a system of mandatory health insurance, which aims to provide universal access to healthcare services for all residents of the Netherlands. It combines elements of both private and public healthcare provision and is regulated by the government to ensure quality and affordability. It covers essential healthcare services, such as primary care, hospital care, mental health services, and prescription medicines. It is primarily funded through premiums, tax revenues, and government grants. The health insurance premium varies depending on the insurance provider and the level of coverage chosen. Additionally, there is an income-related contribution that individuals must pay based on their income. This contribution is collected by the tax authorities. The government pays for children's coverage up to 18 years of age. In addition to basic health insurance, individuals have the option to purchase supplementary insurance for additional coverage, such as dental care, physiotherapy, and alternative medicine. Supplementary insurance is not mandatory and is provided by private insurers.

HTA System

The national HTA body, Dutch National Health Care Institute (Zorginstituut Nederland; ZIN) assess medicines and technologies for inclusion in the Medicine Reimbursement

System (GVS) based on four criteria: effectiveness, cost-effectiveness, necessity, and feasibility. In preparing its advice, ZIN takes into consideration the opinion of a Scientific Advisory Board (WAR) comprising 50 external, independent experts. Other stakeholders such as health insurers, physicians and patient groups are also consulted at this stage. The HTA report is revised based on the feedback received from the WAR and in most cases reassessed by WAR before the recommendations. The recommendations provided by ZIN are also appraised by the Insured Package Advisory Committee (Commissie Pakket; ACP) (see Figure 7). ACP comprises of independent experts appointed by the Ministry of Health, Welfare and Sport (VWS) ranging from clinical practice and patient representation to ethics and health economics.

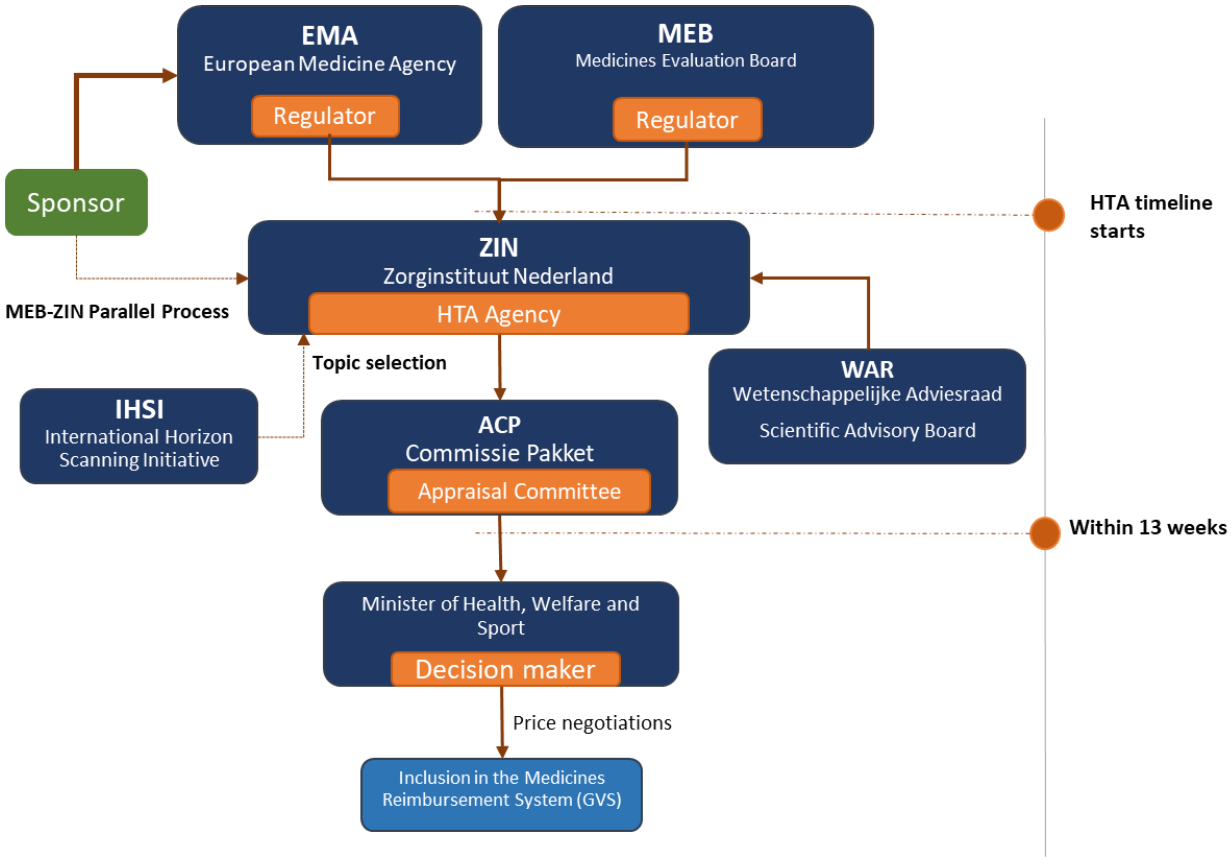


Figure 7 Flowchart of HTA Process in the Netherlands

United States of America (USA)

The USA does not have a universal coverage, although 92% of the population was estimated to have varying levels of coverage in 2018. Health services are funded through public and private, for-profit and non-for-profit insurers. In the public sector, the national government provides funding for health services through the Medicare program, providing coverage for citizens above the age of 65, some citizens with disabilities, veterans, and people on low incomes. The national government also funds various other programs such as Medicaid and the Children Health Insurance Program

(CHIP). There are four levels of coverage included in Medicare for beneficiaries: Part A for hospital insurance; Part B for medical insurance; Part C for the advantage program, under which people can enrol in a private health maintenance organisation (HMO) and Part D for voluntary outpatient prescription medicine coverage. Medicare is funded through general federal taxes, mandatory payroll taxes for hospital insurance (part A) and individual premiums.

At the state level, different states manage and administer varying levels of insurance coverage and safety nets through the Medicaid Insurance program. Through this program, the states can receive federal matched funding to provide healthcare services to low-income families, individuals with disabilities and children up to the age of 18. The eligibility criteria to be enrolled in the Medicaid program can vary from state to state. The Medicaid program is funded through federal tax revenues (63%) and state and local revenues. CHIP is also a public funded but state-administrated program for providing coverage to children from low or middle-income families who may not qualify for the Medicaid program due to income threshold but are unable to afford private insurance.

The dominant form of coverage in the USA is private insurance. Most of the private insurance is employee-sponsored insurance and a smaller share is self-funded insurance purchased individually from for-profit and non-for-profit organisations.

Medicare provides coverage for outpatient medicines through Part D and medicines administrated by physicians under Part B. There is no national HTA organisation or program to broadly assess the health technologies and to inform pricing and coverage decisions. One of the main reasons for this is the decentralised insurance system due to which different public and private payers conduct their own price negotiations and make their own coverage decisions. The HTA elements are incorporated in decision making but it may involve duplicated efforts across different independent organisations. Several independent agencies undertake HTA at a limited level.

At a state level, most of outpatient medicines are dispensed to Medicaid beneficiaries under the Medicaid Drug Rebate Program (MDRP). The state Medicaid agencies, Centres for Medicare, and Medicaid Services (CMS) and participating medicine manufacturers are part of this program. Manufacturers having a National Drug Rebate Agreement (NDRA) under MDRP are responsible for paying rebates to states on a quarterly basis, which is shared between the Federal government and states to offset the overall cost of the medicines for the Medicaid beneficiaries [21]. For prescription medicines under Plan D, the CMS makes a coverage decision through the national coverage determinations (NCDs). When there is no national coverage policy, different Medicare contractors (private insurance providers) make coverage decisions based on a local coverage determination (LCD).

HTA system

HTA in the USA is typically conducted by various organisations at a national and/or State level, including private organisations, and academic institutions.

On occasion, CMS may carry out NCDs to assess whether a particular high-cost or controversial technology is reasonable and necessary for the diagnosis or treatment of a particular disease or injury. These decisions are made through an evidence-based process. In some cases, the CMS assessment is supplemented by externally commissioned HTA undertaken by independent agencies such as the Agency for Healthcare Research and Quality (AHRQ) (for diagnostic tests, surgical procedures, and medical devices) [22]. For specific clinical topics, CMS may also consult the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) which provides independent and expert advice to CMS based on a review and evaluation of medical literature, reviews of technology assessments, and evidence on the benefits, harms, and appropriateness of services that are covered or may be eligible for coverage under Medicare [23]. In some cases, Medicare's coverage requirements, usually based on clinical benefits and potential harms, are different from the FDA's requirements [22]. A recent paper indicated that the FDA usually bases its decision on surrogate end points that likely predict clinical benefit. However, CMS had to deviate from its usual policy of covering FDA-approved drugs in 2022 by specifying that Medicare will only cover monoclonal antibodies indicated for Alzheimer's disease (already receiving accelerated approval from the FDA), if there was evidence of effectiveness from randomised controlled trials. This paper also highlighted that the Inflation Reduction Act 2022 may expand the HTA activities of CMS by requiring it to negotiate prices for selected medicines from 2026 [24].

For LCDs, private insurers may conduct their own form of HTA or use evidence-based evaluations performed by other independent agencies to inform their coverage and reimbursement decisions. The exact process and methods of HTA can vary among different private insurers. For instance, the Institute for Clinical and Economic Review (ICER) is an independent non-for-profit organisation that assesses the clinical and cost-effectiveness of prescription medicines, medical tests, and other health technologies. The ICER evidence reports provide price benchmarks for different technologies based on their clinical and cost-effectiveness, which can be used by individual payers in their price negotiations and coverage decision making. ICER is associated with three independent appraisal committees: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC), and the New England CEPAC, who appraise and make funding recommendations on the ICER assessment reports. These committees meet three to four times each year to vote on evidence presented in ICER's reports. Different stakeholders such as clinicians, patients, and payers can also participate in these meetings to discuss coverage policies.

In some circumstances, individual payers conduct their own assessments such as Blue Cross Blue Shield which reviews technologies in conjunction with the CTAF. The

recommendations provided by the CTAF are appraised by the Blue Shield of California Medical Policy Committee to make coverage decisions.

As discussed above, the Agency for Healthcare Research and Quality (AHRQ) is an HTA agency, but it does not assess medicines.

The methodologies adopted by the different American payers for HTA assessment and appraisal are not very explicitly explained, therefore, for this report, we have focused on the ICER HTA assessment process due to the availability of information.

COUNTRIES WITH SINGLE PAYER HEALTH SYSTEMS

United Kingdom

All the residents in England, Wales and Scotland are entitled to free public health care under the National Health Service (NHS). In Northern Ireland these services are combined under what is known as Health and Social Care (HSC). Like the NHS, the service is free at the point of delivery. The NHS provides healthcare services to all residents of the UK, regardless of their income, employment status, or pre-existing health conditions. Healthcare services provided by the NHS are generally free at the point of use, meaning patients do not have to pay fees or co-payments when accessing most services. This applies to a wide range of medical treatments, hospital care, and primary care services. The NHS is funded by the national government through general taxation and a smaller proportion is derived from payroll tax paid by the employers and employees. Integrated care systems (ICSs) have been recently established as partnerships between all the organisations that plan and deliver healthcare services. A total of 42 Integrated Care Boards (ICBs) have been created within the NHS organisation, replacing clinical commissioning groups. These Boards are responsible for the planning and provision of healthcare services in the ICS area, as well as managing the NHS budget. The Boards, along with the upper-tier local authorities within the ICS area, form a statutory committee known as an Integrated Care Partnership (ICP). This committee brings together different partners to produce an integrated care strategy in the ICS area [25]. The NHS offers a broad range of healthcare services, including primary care provided by general practitioners (GPs), hospital services, mental health care, emergency care, maternity services, and more. Some services, such as dental care and prescription medications, may require patient contributions or co-payments. Moreover, a significant proportion of the population also have voluntary supplementary insurance for access to elective care, including acute conditions and medical tests.

HTA System

England, Wales and Northern Ireland

In England, an independent HTA body (i.e., the National Institute for Health and Care Excellence, NICE) is responsible for conducting the assessment of new health

technologies for their clinical and cost-effectiveness. The 2019 Department of Health and Social Care voluntary scheme for branded medicines pricing and access requires NICE to conduct HTA for all medicines that are new to the UK market or have a significant new therapeutic indication. Medicines which are expected to get regulatory approval are also eligible for HTA assessment. For other topics, NICE produces a list of provisional appraisal topics for technology appraisal guidance that meet the priorities of healthcare system [26]. Many academic and non-academic institutions are involved in informing NICE regarding new and emerging technologies and topic selection.

NICE then identifies bodies representing different key stakeholders including the Department of Health, the Welsh government, NHS England, the company that holds the market authorisation or CE mark for the technology selected for the appraisal and the ICBs. The stakeholders identified as consultees can make a submission to NICE on the technology, as well as provide consultation comments on the draft guidance document. The stakeholder engagements run through the whole HTA process from topic selection to the production of NICE guidance.

Following this, NICE develops a draft scope for each potential evaluation to seek feedback from stakeholders. The draft scope is prepared by identifying key information about the technology through literature searches, confirming the availability of evidence and requesting information from the sponsor. The draft scope is updated based on the feedback received during consultation with key stakeholders and the final scope is then published.

After finalising the scope, the assessment process starts. The company (sponsor) or key stakeholders are invited to submit a comprehensive and concise report on all the available evidence for the evaluation of single technology appraisal (STA), multiple technology appraisal (MTA), cost comparison appraisal (CCA) or highly specialised technology (HST). NICE commissions independent academic groups, called external assessment groups (EAGs), to prepare an assessment report on these evaluations, which is then appraised by an independent appraisal committee that provides provisional recommendations in the form of a Final Draft Guidance (FDG) [27] (Figure 8).

In Wales, the HTA appraisal of new medicines is performed by the All-Wales Medicines Strategy Group (AWMSG). NICE recommendations are applicable in both England and Wales; therefore, NHS Wales will be able to access a medicine if recommended by a NICE HTA process. In cases where NICE conduct an HTA appraisal of a medicine which has already been appraised by AWMSG, the NICE guidance can replace AWMSG''s advice. AWMSG uses the NICE guidelines and criteria to assess the clinical and cost-effectiveness of medicines. The topic selection for HTA appraisal by AWMSG also depends on the future work program of NICE as AWMSG usually does not perform HTA of medicines for which NICE will publish guidance within 12 months of market authorisation.

In Northern Ireland, the HSC is legally required to provide access to medicines recommended by NICE.

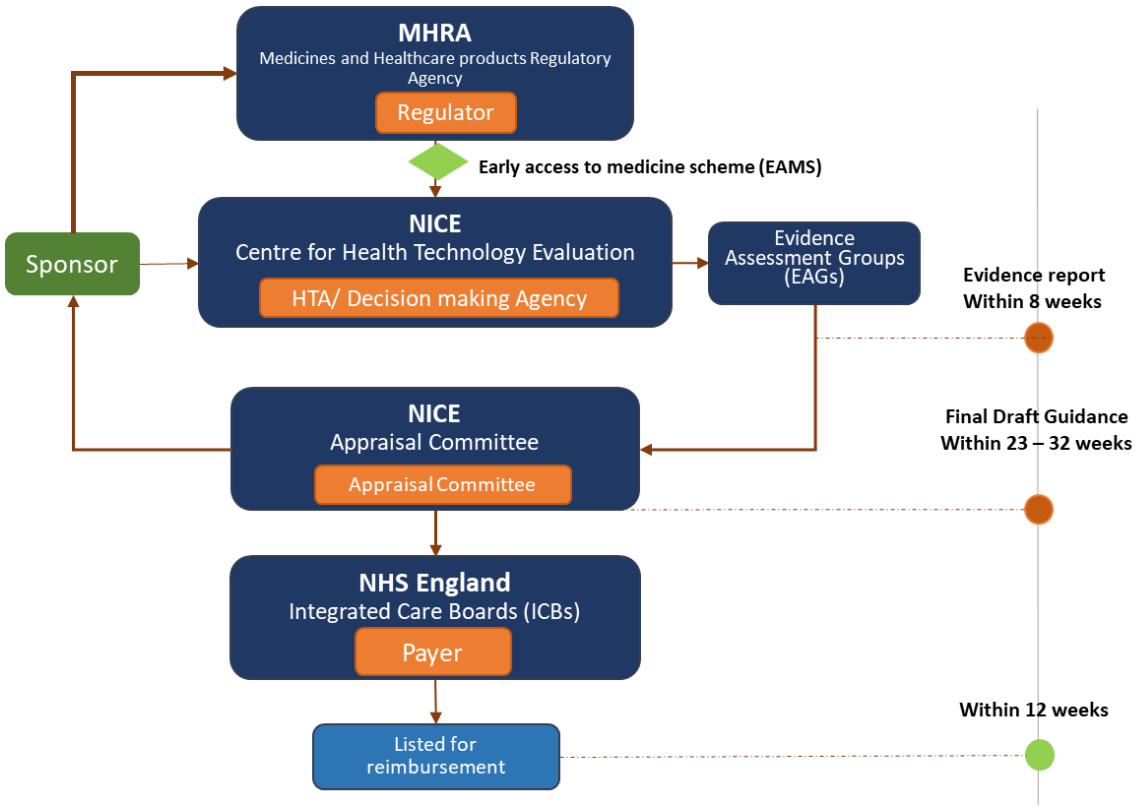


Figure 8 Flowchart of HTA process in Wales and England

Scotland

There are different HTA bodies within Health Improvement Scotland, e.g., the Scottish Medicine Consortium (SMC) and the Scottish Health Technologies Group (SHTG).

The Scottish Medicine Consortium (SMC) provides recommendations to NHS Scotland on the clinical and cost-effectiveness of medicines newly authorised from the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA), new formulations and the new indications for medicines which have already been assessed by SMC.

The Scottish Health Technologies Group (SHTG) consider health technologies such as tests, devices, procedure, digital healthcare programs.

The New Drug Committee (NDC) within SMC carries out HTA appraisal as a response to a submission by a company/sponsor holding market authorisation. The NDC comprises of clinicians, pharmacists and pharmaceutical industry representatives. Members of NDC meet every month to discuss the evidence submitted by the sponsors for each new medicine and testimonies provided by the network of clinical experts across NHS Scotland. NDC provides preliminary advice to the sponsors allowing them to address uncertainties and issues raised by NDC as well as provide feedback before the medicine is considered by SMC. Following this, the NDC recommendations are reviewed by SMC executive consisting of the Chair and Vice Chairs of the SMC and NDC committees, together with SMC senior staff. If a medicine is accepted for use, advice will be issued

to the relevant health boards. However, if a NDC recommendation is negative, sponsors can suggest a new or improved patient access scheme before the medicine is discussed in the SMC meeting, and the SMC executive review will include additional evidence from patient groups. For medicines to treat rare conditions and end of life medicines, sponsors can also request to convene a Patient and Clinicians Engagement (PACE) meeting to incorporate clinicians' and patients' perspectives in the evaluation process (Figure 9) [28].

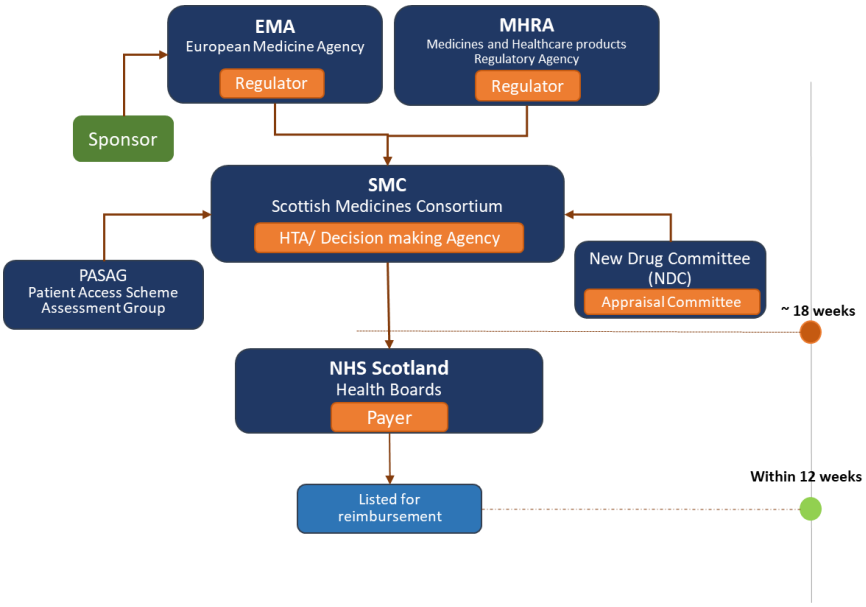


Figure 9 Flowchart of HTA process in Scotland

Taiwan

The Taiwan National Health Insurance (NHI) provides universal and mandatory coverage for 99% of the population. NHI covers comprehensive health products and services, including medicines, vaccines, traditional Chinese medicines, and dental service. NHI is financed by insurance premiums paid by employers, employees and government subsidies [13, 29]. Despite the social health insurance schemes, patients in Taiwan still often face out-of-pocket expenses, including co-payments, deductibles, and costs for treatments or services not covered by insurance. These out-of-pocket payments can be a burden, especially for lower-income individuals. Private health insurance plays a role in subsidising supplementary health care [13].

HTA System

The Center for Drug Evaluation (CDE) is a centralised national HTA agency in Taiwan. The HTA process used in Taiwan is reactive in that the industry sponsors are required to apply to the National Health Insurance Administration (NHIA), and then CDE conduct an assessment in response to the submission. Subsequently the Expert Advisory Meeting (EAM) occurs, where the assessment reports are appraised, and funding recommendations are made by experts attending the meeting. The final decision is

made by the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) joint committee [30, 31] (Figure 10).

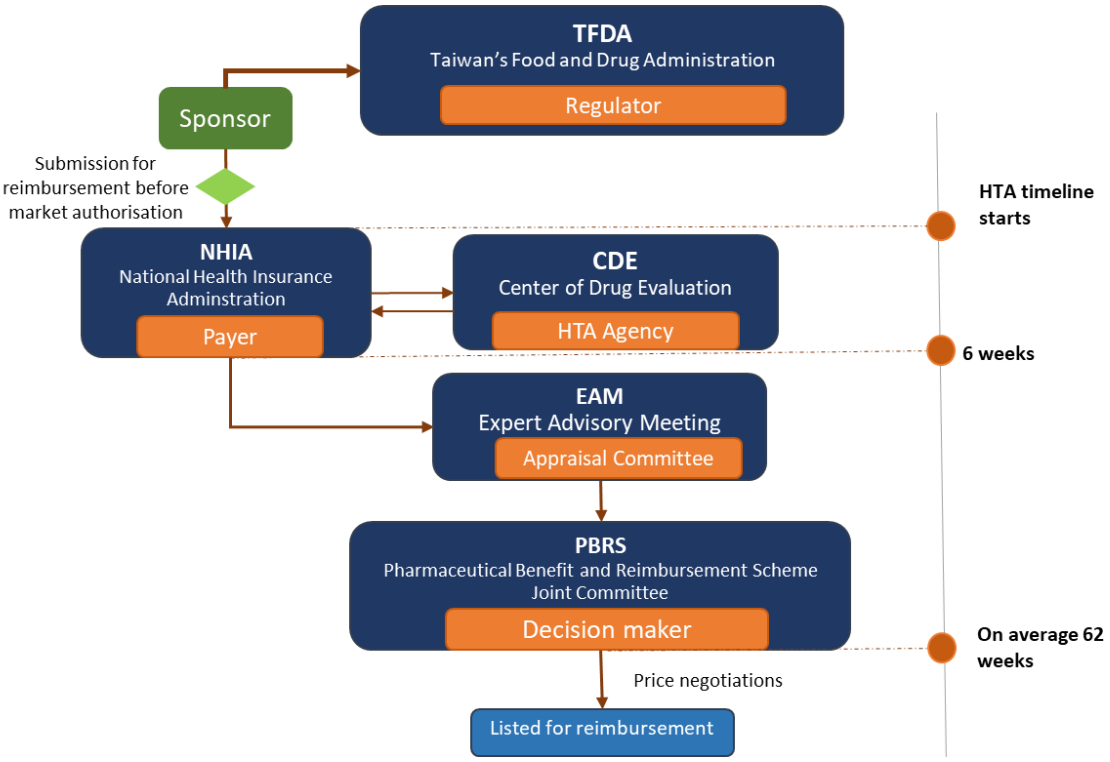


Figure 10 Flowchart of HTA Process in Taiwan

PROACTIVE VERSUS REACTIVE HTA SYSTEMS

HTA agencies can either respond reactively in response to sponsored applications or proactively assess HTA topics that are chosen by public agents and address prioritisation criteria developed for the respective healthcare system.

Most jurisdictions adopt a reactive approach to conduct HTA for medicines. These include Australia, Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Norway, Poland, Quebec, Scotland, Spain, Sweden, Switzerland, and Taiwan. Three jurisdictions conduct HTA proactively: England, Wales, and Japan, along with ICER in the USA, whereas four jurisdictions adopt a hybrid approach: Canada (including Ontario and Alberta), the Netherlands, South Korea, and Singapore.

The reactive process is the same across most jurisdictions, whereby the HTA process is initiated by sponsors from industry. These sponsors are required to submit an evidence dossier for the proposed medicine to be listed on the positive reimbursement list. The proactive HTA model, on the other hand, is based on topic selection. Topics can be nominated by different organisations and stakeholders (except sponsors). The HTA agencies may also conduct horizon scanning to identify emerging technologies, such as in Singapore, the Netherlands, UK and ICER in the USA (note – Canada conducts horizon

scanning but not formally for medicines). The topic can be also directly nominated by other stakeholders, such as the Minister of Health (South Korea), or tumour groups/drug programs (e.g., Canada, including Ontario and Alberta).

In England, Wales, Japan, and America (ICER only), the HTA process is based on a proactive model. For example, for England and Wales, NICE produces a list of provisional appraisal topics for technology appraisal guidance. Many academic and non-academic institutions are involved in informing NICE about new and emerging technologies and topics that should be selected. Topics can be identified through horizon scanning by the National Institute for Health Research Innovation Observatory at the University of Newcastle, as well as relevant companies in the NHS Innovation Service and UK PharmaScan. ICER in the USA, conducts horizon scanning of new and emerging technologies but stakeholders can also submit suggestions for topics to be assessed through a formal HTA. There are some additional criteria for topic selection such as the projected timing of FDA approval within one year, project budget impact, stakeholders' priorities, significance to the public and topics involving vulnerable populations[32]. Japan is an exception, in that topics can only be selected by the Central Social Insurance Medical Council (CSIMC)[33], as the purpose of their proactive approach is to inform price adjustments for an already reimbursed medicine [34]. Medicines are selected for cost-effectiveness evaluation based on the following criteria: 1) medicines that have premiums for added value against the comparator, and 2) medicines with significantly high-cost and/or peak sale JPY 10 billion or more per year. The medicines with premiums that may not have high-cost and/or peak sale JPY 10 billion or more per year may still be selected as a candidate group for evaluation [33].

A hybrid model is used in Canada (including Ontario and Alberta), the Netherlands, South Korea, and Singapore.

In the Netherlands, along with the HTA process being initiated by a sponsor's submission, the HTA agency (ZIN) also actively scans the horizon for emerging medicinal products for decision-makers for planning purposes. As part of international collaborations such as the International Horizon Scanning Initiative (IHSI) and the Beneluxa initiative, ZIN is involved in horizon scanning activities to timely identify forthcoming medicinal products. The aim of IHSI is to make a joint Horizon Scanning database available for all IHSI members. Along with sharing information about the upcoming innovative medicinal products, IHSI also aims to support budgetary policy, pharmaceutical price savings, and provide recommendations for preparing for subsequent HTAs on the topics.

In Singapore, emerging technologies are identified through literature searches and horizon scanning conducted by ACE technical teams. Topics for HTA are also suggested by other sources, such as individual health professionals/public health care institutions or flagged at the meeting where sponsors share their regulatory pipeline with ACE on an annual basis.

In Canada (including Ontario and Alberta) and South Korea, the topic for HTA assessment can nominated by sponsors, cancer speciality groups, patient advocacy groups, regional drug programs (Canada), or the Minister of Health (South Korea). For example, cancer speciality groups can apply to CADTH to start an HTA process. During the assessment, CADTH can also reach out to sponsors to submit data relevant to medicines and their specific indications.

Who conducts the Health Technology Assessment?

Generally, HTA is undertaken in two complementary phases – *evidence assessmen*t and *appraisal*. In reactive HTA systems, evidence assessment for medicines, vaccines and highly specialised technologies usually involves the independent evaluation of an evidence dossier submitted by an industry sponsor who is seeking public funding for the technology. The dossier often includes clinical and economic evidence, some of which may not be in the public domain. In some systems an HTA agency may be commissioned to conduct a systematic review of the clinical evidence and a cost-effectiveness analysis, with or without inclusion of materials supplied by the sponsor [35].

In the *appraisal* phase, the results of the evidence assessment are reviewed by the committee or body tasked with making funding recommendations to a payer/decision-maker. Along with the assessment report, the policymakers/appraisal committees may consider broader aspects in their recommendations such as nature of the innovation, the size of population affected by the conditions, patients and/or clinician's perspective, budgetary implications, and societal value.

HTA assessments in most jurisdictions are conducted by either an in-house government HTA Unit and/or a national independent HTA agency related to the government. National independent HTA agencies are often commissioned by the government to carry out HTA, but they are not a part of the government. In only three jurisdictions (Australia, Japan, and the UK (NICE)), is the evidence assessment purely conducted by external academic HTA groups.

In jurisdictions where HTA is conducted by an in-house government HTA unit, in many cases external HTA experts or an independent HTA agency are commissioned for consultation on the process. For example, the National Insurance Organisation (HVB) in Austria is the in-house government HTA unit, which serves as the major HTA agency to inform medicine reimbursement. But HVB can also commission HTA groups such as the Austrian Institute for Health Technology Assessment (AIHTA) to carry out its own HTA and identify the evidence to use and provide recommendations for reimbursement.

In countries such as Canada, Spain and Italy where provision and financing of health is delegated to regional and/or territorial governments, different regional HTA agencies either independently perform HTA functions or may conduct additional assessments after the advice of the national HTA agency is received. In Canada, all provinces follow the advice of Canada's Drug and Technology in Health (CADTH) except Quebec. Quebec has its own HTA agency, the Institut national d'excellence en santé et en services

sociaux (INESSS), and HTAs within Quebec is conducted by in-house scientific staff in INESSS and members of the l'évaluation des médicaments aux fins d'inscription (CSEMI). In the UK, the assessments can be conducted by independent HTA agencies, such as the National Institute for Health and Care Excellence (NICE), All Wales Medicines Strategy Group (AWMSG), or Healthcare Improvement Scotland/Scottish Medicines Consortium (SMC)), depending on the region they serve. NICE is the overarching HTA agency in the UK, and all jurisdictions, except Scotland, follow NICE guidance when it is available. SMC conducts its own assessment.

Who conducts the HTA Appraisal?

The institutions conducting appraisals often differ from the institution making assessments. In Australia the assessments are done by independent academic evaluation groups, but the appraisal is performed by a separate independent panel of experts.

The recommendations provided by HTA agencies are usually appraised by government-related advisory committees for decision making on medicine reimbursement. In the USA, however, due to the multi-payer system, the HTA assessment and appraisal may be conducted by a payer independently. There is no national HTA agency, therefore, different payers are independent in their decision making. Some institutions such as ICER conduct HTA assessments, however, payers can choose whether to use these assessments in their decision making for funding.

In contrast, there are nine jurisdictions where assessment and appraisal are conducted within the same umbrella institution; these are Austria, Belgium, Canada, Denmark, Finland, France, Italy (national level), Switzerland, and the Netherlands. It is mentioned that although assessment and appraisal are conducted within the same HTA institution in these jurisdictions, there is a separate advisory committee to conduct appraisal within the institution in Belgium, Canada, Italy (national level), Switzerland, and the Netherlands.

Joint HTA Collaborations

There are a few joint HTA collaborations mostly at European level (Table 3). A few of these collaborations are discussed briefly below:

HTA Regulation (EU) 2021/2282

The European Union (EU) HTAR legislation (regulation 2021/2282) is a framework for conducting joint clinical assessment in Europe and was adopted in December 2021. It will take effect from 2025 onwards. It has replaced the voluntary network of cooperation between different member states, EUnetHTA 21 (Joint Actions). The purpose of this new regulation is to facilitate the collaboration and exchange of information between EU member states in the assessment of medicinal products and medical devices, reduce duplication of effort in conducting HTA and promote transparency and patient involvement in the HTA process.

In this joint framework, EU member states will retain their autonomy in determining which medicines they will reimburse. The collaborative efforts will be limited to assessing the clinical effectiveness of medicines and medical devices and will not cover economic, ethical, or organisational aspects, which will continue to be managed at the national level by individual countries. Additionally, member states will participate in Joint Scientific Consultations (including parallel regulatory and reimbursement advice i.e., HTA/EMA) to provide guidance to medicine manufacturers in designing clinical trials with relevant endpoints. Relevant frameworks are being developed which will inform the conduct of Joint Clinical Assessments (JCA) and evidence requirements. The regulation also provides a mandatory mechanism for the submission of evidence by sponsors at EU level. The data submitted to the EU may not be requested again at a national level, although supplementary data can be submitted at the national level.

The implementation of the new legislation will be phased. In the first phase, starting from 2025, the legislation will cover medicines for cancer and advanced therapy medicinal products (ATMPs) such as cell and gene therapy. From 2028, the legislation will cover orphan drugs while all other medicines and certain medical devices will be assessed jointly under this legislation from 2030 onwards.

These reforms imply that some features of national HTA processes, specifically concerning clinical assessment in different EU member states, discussed in the subsequent sections may not be relevant in the future because of the introduction of JCA.

Beneluxa

The Beneluxa initiative was established in 2015 to carry out joint HTA and price negotiations on medicines among member countries, including Austria, Belgium, Ireland, Luxembourg, and the Netherlands. The topics for joint assessment are identified through horizon scanning. All the member countries may not be involved in all steps of the assessment and price negotiations. Even after joint assessment and price negotiations, the individual price and reimbursement conditions are determined nationally. In 2018, the first successful joint assessment was carried out between the Netherlands and Belgium for the spinal muscular atrophy medicine – Nusinersen. The reimbursement conditions differed between the two countries whereas the negotiated prices were confidential.

Nordic Pharmaceutical Forum

The Nordic Pharmaceutical Forum was established in 2015 between Denmark, Iceland, Norway, and Sweden. The purpose of this collaboration was joint assessment and procurement of medicines. As a part of this forum, the first joint process focused on procurement and ensuring the availability of medicines for which it was difficult to find sponsors for the relatively small markets of the member countries, as well as for medicines that have expired patents. As a result of this, procurement contracts were signed for nine medicines for all the member countries.

Table 3 International Collaborations for joint HTA assessments

Name Start date	Countries	Scope	Main objective(s)	Joint key activities	Outcomes/ developments
HTA Regulation (EU) 2021/2282 2022	Austria, Belgium, Bulgaria, Croatia, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungry, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden Observe countries from EEA: Liechtenstein, Iceland, Norway	From 2025: medicines for cancer and advanced therapy medicinal products (ATMPs) From 2028: Orphan drugs From 2030: all medicines	To facilitate the collaboration and exchange of information between EU member states in the assessment of medicinal products and medical devices To reduce the duplication of effort in conducting HTA To promote transparency and patient involvement in the HTA process	Joint clinical assessments, Joint scientific consultations, Identification of emerging health technologies Voluntary cooperation.	Collaborative actions in all activity areas listed
Beneluxa Initiative 2015	Belgium, Luxembourg, Netherlands, Austria (since 2016), Ireland (since 2018)	Mainly new and expensive medicines	To ensure sustainable and timely access to, and appropriate use of, high-quality and affordable medicines in the participating countries	To improve patient access to new and innovative high-cost medicines and therapies To support the sustainability of national health systems To achieve collaboration, leading to synergies between Member States	Joint assessment and price negotiations International Horizon Scanning Initiative
Nordic Pharmaceutical Forum 2015	Denmark, Iceland, Norway, Sweden, Finland (as observer)	Old and new hospital medicines	To provide an informal platform for Nordic collaboration to identify new opportunities, benefit from information exchange and work on joint solutions with a focus on hospital medicines	Horizon scanning, Joint procurement and negotiations, Manufacturing, Logistics, Security of supply	Collaborative actions in all activity areas listed

EFFICIENT HTA PATHWAYS

This section, summarised in Table 4, focuses on:

- The timing of key milestones in HTA pathways, including
    - Time from submission to funding decision
    - Time from HTA recommendations to patient access to funded medicines
- Is there a prioritisation process in these pathways?
- Are regulatory and reimbursement processes aligned?
- Are there any disinvestment processes?

We could not extract data on the number of steps included in HTA pathways as we observed that there was a considerable variation across countries in the composition of each step. For instance, some countries condense different processes into one step, whereas these different processes may be characterised as completely different steps in other countries. Therefore, it was difficult to establish the number of steps due to a lack of standard definition of a step in the HTA process.

Table 4 HTA Pathway elements

Jurisdictions		Timing of key milestones in the HTA pathways*		Number and Type of Steps included in HTA pathways, including prioritisation, disinvestment and alignment with regulatory processes.		
		What is the time taken to reach funding decision (weeks / number of rounds)?	What is the time taken for patients to have funded access to medicines (weeks)?	Does prioritisation occur?	Is there alignment between regulatory and reimbursement processes?	Is there a disinvestment process?
Australia		17-week cycles Multiple rounds possible	No fixed timeline	◑	◑	◑
Austria		Within 26 weeks (< 180 days)	No fixed timeline	○	○	●
Belgium		Within 26 weeks (within 180 days)	○	●	○	●
Canada	CADTH (National HTA agency)	Within 26 weeks	No fixed timeline	●	◑	●
	INESSS (Quebec)	13 weeks – 26 weeks (90 to 180 days)		●	◑	○
Denmark		○	○	○	○	○
Finland		Within 26 weeks	No fixed timeline	○	●	●
France		~ 22 weeks	○	●	◑	●
Germany		24 weeks	0 weeks for patient access 24 weeks – 36 weeks (price negotiation)	●	●	●
Ireland		~4 weeks (RR) ~18 weeks (full HTA)	○	●	●	○
Italy		14 weeks - 26 weeks (100 - 180 days)	No fixed timeline	●	◑	○
Japan		60 weeks – 72 weeks (15 months – 18 months)	~ 9 - 13 weeks (after market-authorisation)	●	○	●
South Korea		21 weeks	Within 39 weeks	●	○	●

Norway		Within 26 weeks	No fixed timeline	●	●	●
Poland		Within 26 weeks	○	○	○	○
Singapore		HTA process initiated by the Sponsor: 20 weeks HTA process initiated by ACE: Expedited assessment: 8 to 12 weeks. Full assessment: 24 to 36 weeks	16 – 24 weeks	●	◑	●
Spain		~ 19 weeks (~ 90 - 95 working days)	○	●	○	●
Sweden		Within 26 weeks	○	●	◑	●
Switzerland		~ 24 – 48 weeks	○	○	○	●
Taiwan, Republic of China		~ 6 weeks for initial HTA (CDE) assessment. On average of 62 weeks from applications to reimbursement decisions	○	●	○	●
The Netherlands		~13 weeks (for reimbursement only)	○	●	◑	○
United Kingdom	Wales	~ 24 weeks	Within 8 weeks	Follows NICE advice		
	Scotland	~ 18 weeks	Within 12 weeks	◑	◑	●
	NICE/NIHR	~ 23 – 32 weeks[1]	Within 12 weeks	●	◑	◑
US	ICER	~10 weeks (for scoping document) Not reported for full HTA	○	●	◑	○

* All timelines have been converted into weeks for consistency, therefore, may differ from the exact number of days or months mentioned in process guidelines for different countries.

[1] The timelines of HTA process in England was verified by NICE on September 13, 2023.

CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

TIME TAKEN TO REACH FUNDING DECISION FROM SUBMISSION

Australia

The Australian HTA process for evaluating medicines at the Commonwealth level contains only a few key steps. These include receipt of an application / submission; independent evaluation of the submission; sponsor response to the evaluation; Economic Subcommittee and Drug Utilisation Subcommittee consideration; sponsor response to the subcommittee summary document; and consideration of all the documents by the PBAC. If recommended, a medicine can be approved by the Minister for Health and Aged Care (or a delegate), or by Cabinet. There are three 17-week PBAC cycles (from submission to PBAC consideration). Major submissions are evaluated by external independent/academic HTA groups during the first 8.5 weeks [10]. Steps between recommendation and listing on the PBS may include negotiations on price, development of risk share arrangements or other conditions. This latter process is not visible, primarily because of the commercially sensitive nature of the discussions.

European Countries

For European countries, the pricing and reimbursement decisions at a national level are structured using a harmonised framework provided by the Transparency Directive (Council Directive 89/105/EEC). One of the purposes of this directive is to ensure a timely and transparent decision-making process across all member state. Article 6 of this directive states that if there is a single or two separate administrative procedures for determining the price of a medicinal product and its inclusion within the list of reimbursed products, the overall timeframe must not exceed 180 days. Under this framework, most member states included in this analysis (e.g. Austria, Belgium, Denmark, Finland, France, Italy, Norway, Poland, Sweden and The Netherlands) make funding decisions within 26 weeks (<180 days) for a single administrative procedure (including both pricing and reimbursement) or within 90 days each when there are separate pricing and reimbursement procedures.

For example, in Netherlands, the national HTA agency, Zorginstituut Nederland (ZIN) is involved in providing recommendations on the inclusion of outpatient medicines in the Medicine Reimbursement System (GVS) [36]. ZIN prepares the recommendations in the form of an assessment report using evidence provided by the sponsor within 2-3 months (~70 days). The Minister of Health, Welfare and Sport (VWS) then takes final decision about whether the medicine is included in the GVS within 20 days. Similarly, in France, the Transparency Council (TC) decides on the inclusion of a medicine on the positive reimbursement list, whereas the Ministry of Health decides on the pricing of the medicine. The national HTA Agency, HAS, provides recommendations to the TC on all new medicines based on whether the actual benefit level is judged mild, moderate, or important within 13 weeks (90 days). There appears to be some variation around this,

though, as one study identified that the overall median time to HTA decision from submission in France is ~22 weeks (157 days) [37]

Germany is one country where the timeline for HTA decisions is not based on the Transparency Directive. Patients can have funded access to authorised medicines (excluding OTC medicines and life-style medicines) at market entry; therefore, the timeline for HTA decisions does not affect their prompt availability. The timeline of the HTA decision, from a sponsor submitting the evidence dossier to the final decision on the added therapeutic value by the G-BA is 24 weeks. In Germany, added therapeutic value is based on the clinical effectiveness of the technology and no cost-effectiveness analysis is performed.

Added therapeutic value has a specific meaning in Germany and is determined using the following criteria. These criteria are applied in a hierarchical stepwise manner, with progression to the next criterion occurring only after the former criterion has been met. If one or more criteria are not met, the evidence is deemed to be not strong enough to prove added benefit and this may lead to the outcome of "no added benefit". [38]

1. Did the pharmaceutical company submit a dossier?
2. Are the included studies acceptable?
3. Is the intervention being compared with the appropriate comparator therapy (ACT) except for orphan drugs? The orphan drugs do not need to be compared to an appropriate comparator (more detail provided in the section 5.5.1)
4. Does the study population reflect the population covered by the label? However, conclusions are also possible for sub-population (e.g., if there are subgroups within the population that fit the label)
5. Is the study duration appropriate?
6. Are the endpoints patient-relevant and acceptable?
7. Is there a benefit? The benefit needs to be clinically relevant, not only statistically.

The information is then assessed on the level of likelihood and extent of added therapeutic value reported. The likelihood is assessed using a matrix comparing the qualitative certainty of the results against the number of accepted studies. The extent of benefit is assessed using a matrix comparing patient-relevant clinical outcomes against whether the effect observed is minor, considerable or major [38].

IQWiG takes a maximum of 12 weeks to carry out their assessment of the submitted evidence and to share their recommendations regarding the additional benefit level of the submitted medicine. Following the publication of the IQWiG assessment, the sponsor is given a hearing, and has the opportunity to submit further data following the hearing, which is then assessed by IQWiG and integrated into final recommendations. In the following 12 weeks, the G-BA assesses the IQWiG recommendations, any additional evidence submitted by the medicine sponsor and then makes the final decision on the additional therapeutic value. If G-BA considers that the additional information submitted following the initial IQWiG assessment could have been incorporated in the dossier, it may not be taken into account. If added therapeutic value

is established, a reimbursement price is negotiated between the sponsor and SHI organisations. The price negotiations must be completed within 24 – 36 weeks.

Another country where the HTA timeline differs significantly from other European countries is Spain. The HTA reports known as Therapeutic Positioning Reports (TPR), were traditionally produced by the Spanish Agency of Medicines and Sanitary Products (La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) and used to take over 9 months with additional time for the input from regional authorities. The TPRs consisted of the clinical assessment conducted by AEMPS and cost-effectiveness was usually not taken into consideration [39]. In 2020, the Spanish Network for the Evaluation of Medicines in the National Health System (REvalMed NHS) was set up to conduct the assessment of the safety, quality, and efficacy of new medicines. It comprised of three main bodies: (a) the Spanish Agency of Medicines and Sanitary Products (La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)) for evaluating the added therapeutic value of the medicines; (b) the General Directorate for Common Portfolio of the NHS and Pharmacy Services (DGCCSF) for conducting the economic evaluation; and (c) three members from autonomous regions (nominated on a rotating basis). The REvalMED-NHS aims to produce an assessment report within roughly 19 weeks through a parallel processing of the therapeutic evaluation by AEMPS and the pharmacoeconomic analysis by the DGCCSF, with input from the autonomous regional communities. This process was piloted in 2021, although it is not clear if it has been adopted as a routine process [40].

Canada

The typical CADTH timelines for all review types, including resubmission and reassessment, is- undertaken ≤ 26 weeks (180 days) from the provision of recommendations. The Ontario and Alberta provinces follow the advice of CADTH for medicine reimbursement; however, Quebec has a separate HTA agency, INESSS, for providing recommendations to the Minister of Health and Social Services on the pricing and reimbursement of medicines. The average time for an HTA decision in Canada is 13 – 26 weeks, although the time to listing varies considerably across the provinces. One study analysed CADTH medicine review recommendations for non-oncology medicines from 2016 – 2019 and found that the average time to patient access to medicines across all provinces was ~ 70 weeks (489 days) from receiving a positive CADTH Common Drug Review (CDR) recommendation. The lowest average time observed was in Alberta at ~61 weeks (429 days) and the highest average was seen in Nova Scotia at ~ 86 weeks (600 days) [41].

United Kingdom

Similar timelines were observed in the United Kingdom, although there are no absolute timelines for different stages of the appraisal process. Timelines can vary depending on the nature and process involved in the appraisal. Typically, the HTA process takes 23 –

32 weeks in the UK (apart from Scotland). Before the HTA process starts, 8 weeks are dedicated for the sponsor to submit a detailed evidence dossier and for NICE to select key stakeholders (clinical, commissioning, and patient experts) and invite experts. The assessment process starts at week 9 and the final draft guidance is produced at week 33 which corresponds to a total period of 24 weeks. The commissioned HTA group, referred to as the Evidence Assessment Group (EAG), has approximately 8 weeks to provide an assessment report to NICE. The sponsors are provided 1 week to comment on the factual accuracy of the report. However, if there is a need to consider evidence gaps and commercial or managed access proposals technical engagement with experts can be arranged this stage. It is not a mandatory stage and, if NICE identifies that the evaluation process will not benefit from additional engagement, then no technical engagement is arranged. In case of technical engagement step, sponsors will have 4 weeks to provide any additional evidence [273].

However, at week 28, if the appraisal committee does not recommend the use of the technology, limits its use beyond what was specified in the market authorisation, or seeks further clarification from the company on the key evidence submitted, a draft guidance document is produced which is open to public consultation for 4 weeks. After considering the comments received, the appraisal committee produces the final draft guidance at week 41 which corresponds to total period of 32 weeks to reach the funding decision [27].

TIME TO PATIENT ACCESS TO FUNDED MEDICINES

Although the time to a funding decision has a similar pattern across countries, there is a much larger variation in the timeline observed from the HTA funding decision to the patient actually accessing the funded medicine. Different factors contribute to these varying timelines, including the time taken for price negotiation, development of risk share arrangements or other conditions between sponsors and payers that are mostly confidential. From 23 countries included in the analysis, seven countries reported having no fixed timelines for patient access to recommended medicines, whereas 12 countries did not report any data regarding the time taken for patients to access funded medicines. Only the United Kingdom (England, Wales, Northern Ireland and Scotland), South Korea and Singapore mentioned a fixed timeline for listing a funded medicine after the HTA decision was made.

United Kingdom

In England, Northern Ireland and Wales, the Health, and Social Care Information Centre (Functions) Regulations 2013 and NICE regulations require that NICE specifies the

[3] The timelines of HTA process in England was verified by NICE on September 13, 2023

timeframe within which the recommendations must be complied with (time to medicine listing from funding recommendations), which in most cases is 12 weeks (3 months). However, NICE can specify a longer period to list the recommended medicine when the medicine is not yet available in England or it cannot be administered properly until certain health service infrastructure and resources are in place, and training is given to the staff for the delivery of the medicine [27]. For innovative oncology medicines, delay in patient access has been addressed through a managed access pathway known as the Cancer Drug Fund (CDF) in England, Northern Ireland, and Wales. Although the CDF recommendations follow the standard NICE evidence evaluation process and timelines, it allows new cancer medications to be funded from the time of final draft guidance publication. This implies that patient can access to new cancer medications 16 weeks earlier than the standard commissioning pathway [42]. The medicine must receive a positive recommendation from NICE (usually a fast-track review) to be considered for the CDF. The launch of the Innovative Medicines Fund (IMF) in mid-2022 applies to non-cancer medicines so that both can now routinely benefit from managed access i.e., be funded earlier while additional data is being collected to resolve any uncertainties. Medicines eligible for these managed access programs must relate to conditions with high unmet clinical need.

In addition, NICE's recent proportionate approach to technology appraisals (PATT) work program allowing faster evaluation approaches for low-risk and simpler treatments. Through this approach, NICE is simplifying and reconfiguring parts of the evaluation process to have more capacity to appraise more medicines. It also involves exploring whether there is a more efficient way to make decisions about whether a medicine should enter a period of managed access, ahead of undergoing a full NICE evaluation. A streamlined decision-making approach was piloted in 5 technology appraisals: nintedanib for treating idiopathic pulmonary fibrosis (8 weeks faster than standard process), eptinezumab for preventing migraine (8 weeks faster), somatagron for treating growth disturbance (7 weeks faster), vutrisian for treating amyloidosis (20 weeks faster), and nivolumab for neoadjuvant treatment of resectable non-small-cell lung cancer (9 weeks faster). The streamlined decision-making approach is estimated to reduce the time in evaluation up to 20 weeks (40%) [43, 44].

Singapore

Singapore is another country which explicitly mentions that medicines receiving positive recommendations must be listed on the Ministry of Health List of Subsidised Drugs (standard Drug List [SDL], Medication Assistance Fund [MAF]) and the Cancer Drug List (CDL) within 16 – 24 weeks (4 - 6 months) of the HTA funding decision. A newer process was introduced in 2021 for new cancer treatments, where sponsors are responsible for providing the evidence to support the HTA decision. The medicines assessed under this new process must also be listed and available to patients within 16 - 24 weeks.

South Korea

In South Korea, the Minister of Health and Welfare is required to make a decision on the reimbursement of a medicine within 39 weeks (270 days) after the submission. After the HTA assessment (within 21 weeks), the price negotiations between sponsors and National Health Insurance System (NHIS) must be completed within 60 days. The NHIS policy deliberative committee within the Ministry reviews the HTA recommendations and price negotiations and provide advice to the Minister within 30 days of completion of the price negotiations [19].

ALLOWING PATIENT ACCESS TO FUNDED MEDICINES BEFORE THE HTA IS UNDERTAKEN

There are two countries (Germany and Japan) where patients can access the funded medicine before the HTA assessment (or cost-effectiveness assessment) is carried out. Germany specifically has the shortest period from registration for patients to access funded medicines. This is achieved mainly by automatic reimbursement of medicines at market entry following market authorisation. For the six months, the company can set the price of the medicine, pending the completion of an added therapeutic value assessment versus a comparator. However, non-prescription medicines, with few exceptions, and lifestyle medicines are excluded from reimbursement. The period of free pricing by sponsors was recently reduced from one year to six months after the introduction of a new GKV Financial Stabilization Act.

In comparison to other countries, Japan only conducts cost-effectiveness evaluations to adjust prices after medicines and medical devices have been listed. The standard timeline for cost-effective evaluation is the longest (60 – 72 weeks) among all the countries reviewed. After the medicine is selected by CSMIC for cost-effectiveness evaluations, it takes nine months for manufacturer analysis, followed by three to six months for academic analysis, and three months of appraisal of the analyses by CSMIC and to make decision [33]. However, patients can access the funded medicines even before the cost-effective evaluation is conducted. A study indicated that medicines are listed on the National Health Insurance (NHI) list after 60 - 90 days of market authorisation, using set pricing rules such as a price benchmarked at the comparator price or using a cost calculation method that sets the price at a pre-set profit rate along with a premium for innovation. It is unclear whether, after the introduction of cost-effectiveness assessment in Japan in 2019, the time to listing has changed, although both are separate processes.

PRIORITISATION

We identified that eight countries have a pathway for early access and prioritisation of certain medicines based on pre-determined criteria.

Countries with Prioritisation Pathways

Swifter paths for resubmissions

In Australia, with the exception of parallel TGA/PBAC process, there is no specific pathway for early access for reimbursement, but PBAC may nominate an early re-entry pathway for resubmissions. It is only applicable for those re-submissions where PBAC considers that residual uncertainty could be easily resolved, i.e. new clinical evidence may not be necessary to support the clinical claim in the resubmission or a revised economic model is not necessary to support economic claims in the resubmission [45].

Like Australia, Scotland allows for the early resubmission of medicines where the only change is a new or improved patient access scheme (PAS). The resubmissions to be considered for this fast-track pathway can only change the list price of the medicine under review [46].

Swifter paths for low budgetary impact medicines

In Scotland, 'me-too' medicines that have low budget impact are eligible for an abbreviated submission to the SMC. This pathway provides faster access to medicines, and helps SMC to make a streamlined decision [47]. The advice for abbreviated submissions will be issued following SMC executive review rather than full committee consideration [48].

Changes in evidentiary requirements

In Canada there are no early access pathways for submissions, however, submissions approved for market authorisation through a Health Canada expedited pathway (such as advance consideration under NOC/c) may be considered for complex review. The complex reviews follow the same timeline as a standard review but differ in the evidence requirements (i.e. non-randomised studies may be considered) and may involve greater consultation with clinical experts and consideration of other potential factors such as ethical and implementation issues [49].

In Taiwan, a medicine can be approved based on surrogate endpoints indicating potential clinical benefit. This reduces the time between clinical trial results and patient access. However, post-market clinical trials are required to verify the presumed effect and sponsors are required to provide their plan for undertaking post-marketing trials [50, 51].

Topic selection

Some countries (England, Wales, Singapore, USA (only ICER) use topic selection process to prioritise the medicines for HTA assessment. The topic is selected through horizon scanning conducted by the HTA agencies or independent academic institutions. For instance, in Singapore topic for HTA assessments are identified through horizon scanning or by stakeholders (clinicians/patients). The identified topics are then prioritised by committees within the Ministry of Health for evaluation by ACE.

The common purpose of topic selection in all these jurisdictions is to choose an innovative and emerging topic for HTA that will add value and support healthcare professionals in providing the best quality care and offer best value for money.

Swifter paths for rare disease and high unmet clinical need

For countries such as Italy, Norway, France and Taiwan, prioritisation is limited to certain medicines, such as for rare diseases and medicines for populations with high unmet clinical need. The process of prioritisation is mostly informed by horizon scanning and will result in priority or expedited review of the selected medicines, reducing the overall time to HTA funding recommendations. In Italy, medicines which are prioritised and assessed through a fast-track process take approximately 100 days. To fast-track access to such drugs, AIFA is required to arrange provision and automatic inclusion into a C-nn class (reimbursement is yet to negotiated) while waiting for the assessment and price negotiations to be completed. During this period, the price of the drug can be set by the market authorisation holder and paid entirely through out-of-pocket payments [52].

From 2021, France also introduced a pathway for early access of innovative medicines following a positive opinion from the French National Agency for Medicines and Health Products Safety (ANSM). The positive opinion is based on the initial results of clinical trials regarding the medicine's safety and clinical effectiveness. There are criteria for medicines to be considered under this pathway: the medicine should be a novel treatment, addressing a high unmet clinical need for a rare or severe disease, treatment initiation cannot be delayed even when the medicine does not yet have market authorisation (MA), and clinical findings must support presumptive clinical benefit as compared to the existing therapy [53]. The early access process follows two pathways: pre-MA and post-MA access. In the pre-MA early access pathway, medicine is available and funded before market authorisation has been granted. HAS decides on early access following a positive opinion from the ANSM, confirming the strong presumption that the medicine is safe and effective. The medicines approved for pre-MA early access must comply with a protocol for data collection and therapeutic use and must submit periodic summary reports of the data collected. The sponsors need to apply for market authorisation within 2 years of applying for pre-MA early access. In the post-MA early access pathway, sponsors can request early access for a medicine based on the above criteria for which market authorisation has been granted but not yet reimbursed. Sponsors may have already submitted, or undertaken to submit, an application to HAS for an HTA assessment. The medicines with post-MA early access also need to comply with a protocol for data collection and therapeutic use, with periodic submission of data summary reports[54].

In France, an ASMR scale is used to rank each medicine compared to existing treatment options. There are five ranks: ASMR I: major improvement; ASMR II: important improvement; ASMR III: moderate improvement; ASMR IV: minor improvement; and ASMR V: no improvement. 20% of the medicines that qualify for early access signify no

improvement in added clinical benefit (ASMR level V) due to a lack of comparative data. As a result, these medicines must be priced lower than the level of their comparators and do not qualify for supplementary funding in hospitals (en sus list). A pilot project was introduced recently to streamline access to innovative medicines that will allow sponsors free pricing up to one year as seen initially in Germany. This will cover medicines that are not eligible for early access due to uncertain clinical and cost-effectiveness and that have an ASMR rating of at least IV.

An Early Access to Medicines Scheme (EAMS) was recently introduced in the UK to provide early access to medicines that do not yet have market authorisation, but which treat life-threatening conditions and address high unmet clinical need. The Medicines and Healthcare products Regulatory Agency (MHRA) provides scientific opinion on the benefits and risks of the medicine and allows patients and healthcare providers to decide whether to access the medicine free of charge before it receives market authorisation. In cases where there is a positive scientific opinion, the EAMS access period is expected to range from 12-18 months. At this stage, NICE may facilitate engagement meetings for sponsors to provide feedback on the evidence required for submission to NICE and discuss managed access and flexible pricing options for the medicine [55].

In Belgium, the early temporary reimbursement (ETR) provides early access to medicines for conditions that satisfy the following criteria: 1) targets an unmet medical need (i.e. included in the list of unmet need); 2) used to treat serious, debilitating or life-threatening conditions; 3) there is no reimbursed alternative; and 4) medicine is included in either a compassionate use program (CUP) or a medical need program (MNP) [56]. Both CUP and MNP programs are for medicines that treat life-threatening disease, chronic disease, and seriously deliberating diseases, and for which there is no alternative treatment available [56, 57]. MNP is for medicines that have been authorised in Belgium but for another indication, while CUP is for medicines that have not been authorised in Belgium. Through the ETR pathway, earlier funded access is ensured either through parallel assessment by the funder and regulator, or through allowing access while a clinical trial is ongoing [56, 57].

The list of unmet needs is created by the General Council in RIZIV-INAMI. A condition can be requested for inclusion on the list by sponsors, College of Medical Directors, and the Minister of Health and the Minister of Social Affairs [56]. In 2016, KCE conducted a pilot study to assess the use of Multi-Criteria Decision Analysis (MCDA) for ranking diseases with unmet medical need. The diseases were ranked according to their therapeutic needs (e.g., impact of disease on quality of life, impact of disease on life expectancy and inconvenience given current treatment) and societal needs (e.g., impact of disease on public expenditures and prevalence of the disease). The median total weighted scores were not aggregated as it was considered inappropriate to weight therapeutic needs against social needs. It is important to mention that this MCDA process was only used to prioritise unmet medical need and was not used as part pf the HTA funding appraisal and deliberative process. Furthermore, it is not clear whether

this pilot project has been adopted as a routine process for prioritisation of unmet need in Belgium.

If a medicine for a specific disease is on the list of high unmet need and it is successfully enrolled in the CUP or MNP, then an application for ETR can be submitted to the Belgian College of Medical Directors (part of NIHDI) [56]. Members from the Commission for Advice on Temporary Compensation for the costs of a pharmaceutical product (CATT/CAIT) appraises these medicines using the same HTA methods as done normally for medicines in Belgium [56]. The College of Medical Directors makes the final decision, which is called a "cohort decision", and includes the conditions for level of reimbursement, the patient cohort eligible for ETR, and the budget needed to cover the products [56]. Cohort decisions are time-restricted and the budget is defined yearly [56].

ALIGNMENT BETWEEN REGULATORY AND REIMBURSEMENT PROCESSES

To provide timely recommendations for reimbursement of medicines by HTA bodies and reduce the time of patient access to new medicines, 41% jurisdictions (n = 11/27) have a parallel regulatory and HTA process. This allows sponsors to submit the HTA dossier for assessment while the medicine is under review by the regulatory body for market authorisation. However, it is possible that there is only partial alignment between these processes as no formal data sharing was mentioned between the regulatory body and HTA agency in these countries.

Australia

In Australia, a parallel review process was introduced in 2012, where sponsors can submit an HTA dossier to PBAC while a regulatory application is considered by the regulator, the TGA.

A recently reported study by Merlin et al (2023) found that, since 2012, 43.4% (n = 79) of Public Summary Documents concerning oncology medicines involved submissions that used the parallel process [58, 59]. 90.0% (n=45) of parallel submissions used the same pivotal evidence to inform both TGA and PBAC decisions as compared to 77.5% (n=55) undergoing the sequential process. There was no difference in the quality of evidence in submissions irrespective of whether they were submitted through the parallel or sequential process. On average, across 152 oncology medicine submissions, PBAC had made their decision 17.5 weeks before TGA registration on the Australian Register of Therapeutic Goods (ARTG) for those submissions undergoing the parallel process, whereas it was 50 weeks after ARTG registration for submissions undergoing the sequential process. This means that if a medicine is funded at first consideration by PBAC that parallel processing in Australia can reduce the evaluation and appraisal phase of the HTA process by 67.5 weeks ($p<0.01$) (see Figure 11). It should, however, be noted that there is a high rejection rate at initial consideration of oncology medicines (59.9%

between 2012 and 2021) and so for unsuccessful submissions, although the evaluation and appraisal phase is faster for those processed in parallel between the TGA and PBAC, several resubmissions may still be required prior to achieving a positive funding decision [59].

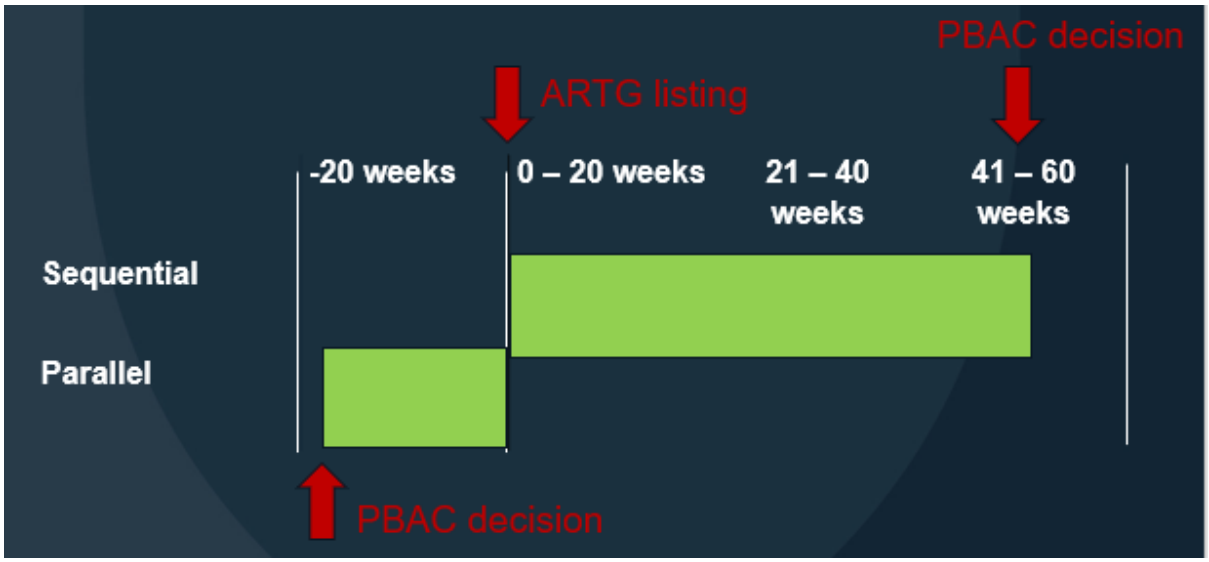


Figure 11 Time to PBAC funding decision from market access listing on the Australian Register of Therapeutic Goods (ARTG) for oncology medicines undergoing either sequential or parallel processing in Australia

Source: Merlin et al 2023 ([59]).

Canada

A parallel regulatory and reimbursement process exists in Canada, but it differs from Australia in that a notification of a submission prior to receiving market authorisation from Health Canada (i.e., pre- Notice of Compliance (NOC) submissions) may be filed up to 180 calendar days in advance of the anticipated receipt of an NOC or NOC/c (Notice of Compliance with conditions (NOC/c). Similarly, INESSS accepts registration/listing requests for medicines awaiting a NOC from Health Canada i.e., for a new or already listed drug, cellular therapy, gene therapy, advanced therapeutic product, or radiopharmaceutical product. The granting of the Notice of Compliance must be expected within the next 180 days.

United Kingdom

England and Wales

NICE will not provide guidance on any technology that has not received market authorisation in the UK. However, as discussed in previous section, the topic selection, HTA scope development, and evidence generation for early access pathways can be initiated before market authorisation. This enables NICE to publish HTA assessment guidance very close to market launch [60].

Scotland

In Scotland, the market authorisation and the HTA process are partially aligned for medicines that address a high unmet clinical need for life-threatening and highly debilitating conditions. SMC allows interim acceptance for medicines that have been given early or conditional market authorisation by MHRA, but future access to these medicines depends on ongoing re-assessments. When an issue regarding medicine effectiveness is raised by the MHRA, the interim access is terminated. A full submission to SMC is needed if the conditional market approval is to turn into a full market approval [61].

France

A similar process is followed in France where early access authorisation is available for innovative medicines indicated for severe, rare, and highly debilitating diseases with no appropriate treatment available. As discussed in the previous section, this follows two pathways: pre-MA early access, for medicines for which sponsors have already submitted, or undertake to submit within one month for market authorisation once early access has been granted. The French National Agency for Medicines and Health Products Safety (ANSM) and HAS decide on pre-MA early access only after confirming the potential efficacy and safety of the medicine based on the results of the clinical trial. The other pathway is post-MA early access for medicines, with market authorisation granted but not yet reimbursed within the common law framework. The patient can access the medicine while the medicine undergoes the HTA [62].

The Netherlands

In the Netherlands, a MEB-ZIN Parallel Procedure was launched in April 2019 condensing the market authorisation phase performed by European Commission (EC) and Medicines Evaluation Board (MEB) as part of the EMA and reimbursement approval phase performed by ZIN. In this parallel process, the sponsors can start the submission to ZIN 30 days earlier in comparison to sequential process. Aside from this, the phases of the market authorisation and reimbursement approval remain unchanged [63].

United States of America

Similarly, ICER in the USA begins its assessment process approximately 8 months before the expected decision on the market authorisation approval by the U.S. Food and Drug Administration (FDA). The purpose is to ensure that the final report and public hearing aligns with upcoming FDA decisions, when paying bodies such as insurance companies or CMS take initial coverage decisions and negotiate prices [32].

DISINVESTMENT

The information on disinvestment processes for medicines is limited. The information was mostly extracted from the peer-reviewed literature as we could not identify this information in HTA process guidelines and/or methodologies. Our data indicated that very few countries have a consistent process that is used to disinvest low-value or obsolete health technologies. For countries where there is a process, it is mainly price readjustment through periodic re-assessment of the listed medicines.

Australia

For medicines listed on the PBS, there is no published HTA process that is used to guide disinvestment HTA. Disinvestment may occur indirectly through regulatory actions (removal of the medicine from the market), or through withdrawal by the sponsor (as may occur if clinical practice ceases to use the medicine). The Australian Government may undertake or contract out reviews of currently listed medicines (e.g., PBS Post-market reviews) to ensure their ongoing cost-effectiveness; however, this is not a regular feature of the current HTA process for medicines.

Countries with a fully/partial disinvestment process

European Countries

Major European countries did not report any consistent disinvestment process that is part of the HTA process for medicines.

For instance, like PBAC, TLV in Sweden occasionally initiates a review of medicines' pricing and reimbursement status. The purpose of such reviews is to assess whether the reimbursed medicine is still providing the value indicated in the original HTA report. As a result, low value or obsolete technologies are either excluded from the reimbursement scheme or undergo restricted reimbursement (for a specific population(s)) or a lowering of the price [64].

One of the policy documents from HAS (France) mentioned that periodic reassessments may occur after every 5 years for all medicines listed for sale by community pharmacies. As a result of this reassessment, the TC provides an updated recommendation to the Healthcare Product Economic Committee which can result in price renegotiations and/or disinvestment. It is unclear whether this process still exists, as this document is from 2014 and no updated information is available on the HAS website.

Switzerland is one of the countries where there is a consistent disinvestment or reassessment process referred as 'Triennial Review' i.e. it is conducted every three years by Federal Office of Public Health (FOPH) to determine whether the medicines listed in the List of Pharmaceutical Specialties (SL) still meet the requirements for listing. The medicine prices are readjusted, or changes may be made in the conditions

of the listing and in some cases, medicines may be completely delisted because of these reviews.

United Kingdom (except Scotland)

In the UK (except Scotland) disinvestment may occur through routine surveillance of the NICE recommendations due to loss of market exclusivity. In cases when generic medicines or biosimilars are licensed for the same indication, NICE can initiate a review of its original recommendation which may result in disinvestment and/or a price readjustment [27].

Taiwan

A study mentioned that in Taiwan, the reimbursed price is adjusted based on a market survey periodically conducted by the NHIA [65]. However, we could not verify this information from any policy or HTA process document available in English [65].

FLEXIBILITY, PREDICTABILITY AND TRANSPARENCY OF HTA PATHWAYS

This section focuses on three main factors of HTA pathways that are important to stakeholders, particularly to industry and patient groups, flexibility, predictability and transparency (see Table 5).

Defining flexibility

The flexibility of the HTA process was assessed with reference to HTA appraisal (decision) and HTA evaluation. Traditional binary HTA funding decisions (funded or not funded) may not fit the needs of payers when the evidence is uncertain. The HTA outcome was considered flexible if the HTA outcomes are not binary or if medicines could be listed with conditions (managed entry agreements/reimbursement with conditions). HTA appraisal was considered as partially flexible if the conditional approvals were only for specific technologies (e.g., medicines for rare diseases).

The flexibility of the HTA evaluation process was judged by whether there are fixed HTA cycles and pre-determined HTA steps. The HTA cycle is defined by the frequency of committee meetings and the time allowed for submissions. HTA cycles can be pre-defined and follow the same pattern each year, or the assessment can be initiated at any time based on when the submission is received. HTA might also be conducted within a given fixed period, in which the time given to workflow through each step is fixed. The HTA evaluation process was considered flexible if there was no fixed HTA cycle and no fixed HTA steps/process. HTA evaluation was considered partially flexible if one of these aspects was not fixed.

Defining predictability

Predictability is essentially the obverse of flexibility. A decision on the predictability of HTA evaluation was made based on whether the HTA method and submission guidelines were available for all stakeholders. It was considered partially predictable if only one of these documents was available.

HTA appraisals were considered predictable if process guidelines explained how, or which specific, factors lead to specific HTA recommendations, such as utilising Multi-Criteria Decision Analysis (MCDA). The factors we considered that make outcomes more predictable for stakeholders included evidence characteristics, weights, and decision-making thresholds. HTA recommendations were considered partially predictable if some factors such as specific decision-making thresholds were mentioned but where it might still not be possible to predict the HTA outcome with certainty.

Defining transparency

We evaluated the transparency of HTA on an Evidence-to-Decision basis [66], where the availability of information relevant to both assessment and appraisal processes was considered. In this report, the transparency of HTA was evaluated from two perspectives: sponsors and other stakeholders (including the public). If sponsors can participate in the HTA process by accessing and/or commenting on the assessment/appraisal reports or can directly participate in the committee meeting, the HTA process was considered transparent for the sponsor. It may also involve two-way communication between sponsors and HTA agencies for clarifications and/or requests for additional evidence. For other stakeholders, such as patients, if the assessment, appraisal, and other decision-related documentations were available without any redaction, the HTA process was considered transparent. If HTA reports and other relevant documentations were published on a payer/HTA agency website with commercial or academic information redacted, the HTA process was considered partially transparent.

The stakeholder engagement in the HTA process is further discussed in detail in *Stakeholder Involvement in the HTA pathways* on page 100.

Table 5 HTA Pathway outcomes

Jurisdiction		Is the HTA process flexible?		Is the HTA process predictable?		Is the HTA process transparent?	
		Is there flexibility in the HTA appraisal (decision-making) step?	*Is there flexibility in the HTA evaluation step?*	*Is there predictability in the HTA appraisal (decision-making) step?*	*Is there predictability in the HTA evaluation step?*	*For Sponsors*	*For all other stakeholders (including patients and public)*
Australia		●	●	●	●	●	◑
Austria		●	○	○	○	○	○
Belgium		◑	○	○	○	○	○
Canada	CADTH (national HTA agency	●	●	◑	●	●	◑*
	INESSS (Quebec)	●	●	◑	◑	○	○
	Ontario (HQ)	Follow CADTH					
	IHE (Alberta)	Follow CADTH					
Denmark		◑	○	○	○	○	○
Finland		●	○	●	◑	○	○
France		●	○	●	●	○	○
Germany		●	●	◑	●	●	●
Ireland		◑	○	◑	●	●	◑
Italy		◑	○	●	●	○	○
Japan		●	●	◑	●	●	◑
Norway		●	○	●	●	●	◑

Jurisdiction		Is the HTA process flexible?		Is the HTA process predictable?		Is the HTA process transparent?	
		Is there flexibility in the HTA appraisal (decision-making) step?	*Is there flexibility in the HTA evaluation step?*	*Is there predictability in the HTA appraisal (decision-making) step?*	*Is there predictability in the HTA evaluation step?*	*For Sponsors*	*For all other stakeholders (including patients and public)*
Poland		○	○	○	○	○	◑
Singapore		◑	●	●	●	●	◑
South Korea		◑	○	○	○	○	○
Spain		○	○	●	●	●	◑
Sweden		●	○	●	●	○	◑
Switzerland		●	○	○	○	○	◑
Taiwan, Republic of China		○	○	○	○	●	○
The Netherlands		◑	●	◑	●	○	○
United Kingdom	Wales	Follow NICE					
	Scotland	●	◑	●	●	●	◑
	NICE/NIHR	●	◑	◑	●	●	◑*
USA	ICER	◑	○	○	●	●	●*

* NICE, ICER and CADTH have recently signed a joint transparency agreement for not redacting clinical data that are awaiting publication when they publish their respective decisions or recommendations [67].

CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Flexibility of HTA process

Australia

The HTA evaluation process is not very flexible in Australia. Although there might be special meetings, PBAC has a very fixed meeting agenda, which happens three times a year in March, July, and November and the evaluation must occur within those cycles. From submission to HTA funding recommendation, the HTA cycle comprises of 17 weeks, with 8.5 weeks for the commissioned HTA group to carry out the assessment of the submitted evidence [68]. The HTA appraisal process, on the other hand, is flexible, as in cases where PBAC has equivocal confidence in the extent of clinical or cost-effectiveness of the medicine due to uncertainty associated with the evidence submitted, the government may decide to subsidise the medicine using managed entry agreements (MEAs) (e.g., risk-sharing agreements). The MEAs are part of government initiatives to encourage early dialogue with sponsors to address areas of uncertainty. The sponsor, the government or the PBAC can request the MEAs. The PBAC guidelines indicate that a submission would be considered for an MEA if PBAC accepts that there is a high clinical need for the drug and new evidence will resolve the uncertainty regarding the value or extent of the clinical and cost effectiveness that would have otherwise prevented an initial positive recommendation.

Jurisdictions with flexible HTA processes

We identified five jurisdictions (Austria, Canada, France, Japan, Switzerland, UK) where HTA outcomes are not limited to positive and negative recommendations, but allow conditional reimbursement based on clinical need.

HTA assessments in France and Austria can result in a recommendation of different reimbursement levels. In France, HTA assessments are based on two aspects; clinical added value (ASMR) and clinical benefit (CB)[69]. There are five ranks: ASMR I: major improvement; ASMR II: important improvement; ASMR III: moderate improvement; ASMR IV: minor improvement; and ASMR V: no improvement. The level of ASMR defines the framework for price negotiation. CB determines the reimbursement rate, categorised as insufficient, mild, moderate, or important. An insufficient CB results in a medicine not getting listed. However, while there is flexibility in decision-making, the HTA cycles are fixed and predictable. A committee meeting is held every two weeks [70].

In Austria, the level of HTA recommendation is reflected by the code of reimbursement (EKO) [71], which categorises medicines according to colour – there are different "colour boxes (green, light yellow, dark yellow, and red box)". For example, medicines in the green box indicate an unrestricted listing to prescribe, whereas medicines in the red box can only be reimbursed after a maximum of 180 days, and reimbursement requires approval by chief medical officers of the health insurance bodies to be prescribed.

In the UK, Canada and Switzerland, medicines can be conditionally approved to manage the uncertainty in the evidence. These medicines may be recommended for a limited population and/or indication or may have other arrangements put in place such as managed entry agreements (MEA), or price reductions. For instance, in Canada, if the medicine demonstrates added comparative clinical benefit, but the cost-effectiveness is unacceptably high, the medicine may be reimbursed on the condition that there is a price reduction [49]. CADTH committee meetings are held 12 times a year but the HTA cycle under INESSS (Quebec) remit is very flexible. To collaborate better with CADTH, INESSS (Quebec) has also started to use a continuous mode of assessment instead of their previous three times a year[72].

In UK (NICE), there are different recommendation levels for medicines – they may be recommended, recommended in specific circumstances, recommended with managed access, and recommended only in a research context [27]. Moreover, some medicines may be reimbursed by NICE and SMC (Scotland) for a limited period under manage access schemes while evidence is being generated [61]. However, the timelines of each procedure are fixed and pre-defined.

Jurisdictions with partially flexible HTA process

Some jurisdictions (Belgium, Denmark, Germany, Finland, Italy, Ireland, South Korea, Singapore, Sweden, and the Netherlands) mentioned having flexible HTA outcome for a specific use of medicines such as for rare diseases. Different jurisdictions apply different criteria, such as satisfying high unmet clinical need, orphan drugs, medicines with uncertain long-term benefits, etc. Due to small patient population, uncertain long-term effects, considerable budget impact and other issues, specific medicines may be conditionally reimbursed with the requirement of further evidence development. The consequence of failing to meet the requirements of reimbursement might be delisting or disinvestment, depending on the agreement struck.

In Belgium (KCE remit) and Germany, the HTA outcomes may be partially flexible while the HTA cycle is fixed. In Belgium (KCE remit), there is an annual HTA cycle, and there is a specific time to call for a topic each year. The working agenda is set on an annual basis. On the other hand, in Germany sponsors are required to initiate a HTA application within three months of a medicine obtaining market access.

Predictability of HTA process

Australia

The timing of the PBAC process and the criterion for assessment are predictable. There are detailed submission and assessment guidelines available on the PBAC website, which make it easy for sponsors and other stakeholders to identify the steps and nature of the assessment involved in the development of HTA reports and commentaries. However, while the decision-making process refers to key criteria that influence PBAC

decisions, the weight of these criteria and the threshold at which decisions would change from reject to recommend is unclear. As a sponsor, it is not possible to predict with certainty what medicine price would result in a recommendation or to what extent specific characteristics of the evidence (such as equity considerations, uncertainty in the magnitude of the effect, applicability, populations with high unmet clinical need) would influence the price that is regarded as cost-effective by the committee.

Jurisdictions with predictable HTA evaluation steps and partially predictable HTA recommendations.

Most of the jurisdictions with available documentation have predictable HTA processes but do not have fully predictable HTA funding recommendations. Jurisdictions include Canada, Germany, Ireland, Japan, the Netherlands, and the UK(NICE). For these jurisdictions, the guidelines that assist sponsors in preparing submissions are clear, and the methods of doing the HTA are transparent to the public. The HTA appraisal and funding recommendations are, however, partially predictable. Although some jurisdictions mention decision-making threshold (such as an ICER threshold), it is difficult to determine the extent to which specific evidence characteristics contribute to the decision. No jurisdiction mentioned using tools such as MCDA on a regular basis in all of their HTA assessments, which suggests it might not be practical or useful for decision-making. Further information on this issue is given in Paper 4 – Clinical evaluation.

We noted that willingness to pay (WTP) is one factor that is associated with the predictability of HTA recommendations. Unlike Australia, some countries use an explicit ICER or WTP threshold in decision-making, although, in some cases the medicines may still be reimbursed even if the ICER is above the recommended threshold. In Ireland, the WTP is EUR45,000 per quality-adjusted life-year (QALY)[73], and in the UK, it is £20,000 to £30,000 per QALY [27]. Generally, ICERs below the lower interval is considered cost-effective whereas medicines above the upper bound is not considered cost-effective. For submissions with ICERs above £20,000/QALY, additional factors such as the nature and extent of innovation in the technology, uncertainty surrounding ICER value and health utility not fully represented in the ICER estimation are considered important for the decision making. Modifiers are applied to weight the ICER. Medicines meeting severity criteria can be recommended with an ICER threshold higher than the conventional ICER range. This reflects the importance of social value judgements in NICE deliberation process [74].

In the Netherlands, disease severity is scored in a range from 0 to 1, with a severity score of 0.10 - 0.40 associated with a WTP of EUR20 000 per QALY, 0.41 - 0.70 associated with a WTP of EUR50 000 per QALY, and a severity score of 0.71 - 1.00 associate with a WTP of EUR80 000 per QALY [75]. Application of this threshold is dependent on other clinical factors such as high unmet clinical need and so may not make an HTA recommendation fully predictable.

Jurisdictions having predictable HTA evaluation steps but unpredictable HTA recommendations.

Jurisdictions such as France, Singapore, Italy, Sweden, Spain, Norway have predictable HTA evaluation steps but unpredictable funding recommendations.

In France [69] and Singapore [76], the factors influencing decisions are provided, but just like in Australia, the weight of these criteria and the threshold at which decisions would change from rejection to recommendation is unclear. Although, there is no threshold for decision-making in France, there is a matrix of how HAS would consider health impact. For example, the clinical need for medicines is measured by the prevalence of the disease and the seriousness of the disease, and whether there is an alternative in the market or not. A medicine cannot be considered as satisfying "unmet need" when the disease has a high prevalence (more than 1 per 2,000 cases), and there is the existence of a clinically relevant comparator. Although sponsors are unable to predict the recommendation, the matrix gives sponsors extra information on how the medicine is valued.

The HTA evaluation steps in Belgium (KCE remit) and the US (ICER remit) are predictable, given the methods are published. However, the HTA assessment might not necessarily inform the final HTA recommendations for all the payers. Therefore, we are unable to assess the predictability of the HTA appraisal process.

Transparency of HTA process

Australia

Decisions made by the PBAC are completely transparent for sponsors and partially transparent for other stakeholders. Sponsors are provided the opportunity to respond to the assessment report (commentary and ESC advice) within 1 week of it being considered by PBAC or its technical subcommittees. For other stakeholders, including patients and public, the key areas of concern are publicly disclosed. However, public summary documents commonly contain redactions of key information, including both clinical and economic evidence.

Jurisdictions with partial/fully transparent process

We identified that most jurisdictions (Australia, Belgium-KCE, Canada-CADTH, Ireland, Japan, Norway, Singapore, Spain, Switzerland, UK, USA) have fully or partially transparent HTA processes. The HTA in most of these jurisdictions is transparent to the sponsor and partially transparent to other stakeholders including patients and the public. Full transparency to sponsors and all other stakeholders only occurs with ICER (USA) and KCE (Belgium) but in both cases the assessment might not directly inform the funding decisions of their payers.

Most of the HTA reports relevant to funding decisions are summarised and published with an account of the assessment and the HTA funding recommendations. However,

the amount of information and the proportion of redaction in documents differ across countries. For example, unlike the Public Summary Documents published by PBAC, the risk of bias of included clinical trials and inputs of economic model are not available in the public accessible document in Ireland.

In countries like the UK, the appraisal committee meetings are mostly open to the public and sponsors except when committee decisions are taken by a subset of an appraisal committee. These sub-committee meetings are outside of the main committee and therefore cannot be attended by the public or stakeholders. The main appraisal committee meetings can be attended by academics, patient advocates, industry representatives and other stakeholders. They can also submit their statements to NICE. These committee papers are published along with the final draft guidance document. The confidential information, however, is removed before publication.

Recently, CADTH, NICE and ICER issued a position statement indicating greater transparency of unpublished data in their recommendations and decisions. Under this arrangement, from May 2023, CADTH and NICE will not redact any clinical data that are awaiting publication in their documents. ICER will allow redaction of data that is agreed to be published publicly for 12 months as academic in confidence [67].

NICE also publishes a plain language version of its recommendations known as 'Information for the Public'. In the past, NICE has accepted the unpublished data as evidence under a confidentiality agreement. Such evidence comprises of academic-in-confidence (public disclosure would limit the ability to publish the evidence in scientific literature) and commercial-in-confidence (public disclosure impacts the commercial interests of a company). The academic-in-confidence evidence can be presented at an appraisal committee meeting attended by members of the public. Moreover, the company/sponsor representatives participate at the committee meeting but do not have access to any confidential information or the appendix created by the External Assessment Group for an evaluation against a comparator that is under-confidential commercial arrangement [27].

For some jurisdictions (Belgium; NIHDI remit), France, Poland, Switzerland (The Health Insurance Benefits Division remit), Sweden, Switzerland, Taiwan, and the Netherlands, it was difficult to establish the transparency of the HTA process as published reports were not available in English. The published reports suggest a certain degree of transparency, although, we cannot establish the extent of this based on the published information.

STAKEHOLDER INVOLVEMENT IN THE HTA PATHWAYS

Literature included in the scoping review was able to populate most of Table 6 (see below). However, as the 'not reported' cells show, roughly half of the included jurisdictions (15/27) did not report any concerns or consideration of geographic or socio-economic equity ('not reported' in the 'Geographic' and 'Socio-economic'

columns). It is unclear whether this reflects such concerns being absent in those jurisdictions, or simply incompleteness or opacity in the sources that describe and study these jurisdictions. It may be the latter, in that most jurisdictions (22/27) did report some concern for equity, with it being mentioned either generally or in relation to a specific factor (such as severity, age and end-of-life setting). Few jurisdictions reported whether they promoted equity or engaged stakeholders in the case of specific technologies (such as medicines for rare diseases or cancer), where distinct pathways sometimes existed apart from a jurisdiction's general HTA processes. Only roughly half of the jurisdictions (15/27) explicitly reported engaging academia as part of their general HTA, though the more ambiguous term 'expert' was very often used. This could encompass a clinical or academic expert, so was categorised under 'Other'.

Stakeholder engagement is clearly widespread in HTA. The specific stakeholder most consistently engaged was industry (23/27), often in the form of being permitted or invited to submit applications for the funding of medicines. Clinicians were the next most consistently engaged stakeholder (22/27), often to provide clinical expertise on the medicine or evidence base. They were followed closely by patients and their representatives (including carers, families and patient organisations) (21/27), who were often engaged to supplement (less often to shape) the evidence base, with reports on patient experiences and intervention outcomes that mattered to them. The importance of Patient-Reported Outcomes (PRO) is increasingly emphasised, especially in Europe, although the active collection and use of these in HTA appears very limited [77], and there are mostly only pilot projects of patient preference elicitation studies (usually discrete-choice experiments) [78].

A large swathe of the scholarly literature reviewed for this paper (roughly one third) focussed on patient engagement, clearly indicating that this has been a prominent topic within HTA scholarship in the past 10 years. In recent years, HTA agencies seem to be increasingly active in their engagement, especially with patients. Jurisdictions creating or renewing their HTA processes may be turning to the scholarly literature for guidance, then finding and acting on the increasing volume of published material on patient engagement. Comparatively little of the included scholarly literature focussed on equity in HTA (though there is a separate, often theoretical literature on equity within broader health ethics and health economics literatures, which may suggest something of a theory-practice gap).

Table 6 Involvement of different stakeholders

Jurisdiction		Does the HTA process promote equity?				Engagement in the HTA process?						
		Geographic	Socio-economic	Other	For specific technologies	Patients and patient organisations	Members of the public	Industry	Clinicians	Academia	Other	For specific technologies
Australia		●	●	●	◑	●	●	●	●	◑	●	◑
Austria		●	●	●	○	●	●	○	○	●	●	◑
Belgium		◑	●	●	●	●	●	●	●	●	●	●
Canada	CADTH (national HTA agency)	●	○	●	●	●	●	●	●	●	●	●
	INESSS (Quebec)	●	○	◑	●	◑	●	●	●	●	●	●
	HQO (Ontario)	◑	●	●	●	●	◑	●	●	◑	●	●
	IHE (Alberta)	○	○	◑	●	●	●	●	●	●	●	●
Denmark		○	○	◑	○	●	◑	●	●	●	●	○
Finland		●	●	●	●	○	●	●	●	○	●	○
France		●	●	●	○	●	●	●	○	○	◑	○
Germany		○	○	●	○	●	●	●	●	●	●	○
Ireland		○	●	●	○	●	●	●	●	●	●	○
Italy		○	○	○	○	◑	○	○	○	○	○	●
Japan		●	●	●	◑	●	◑	●	●	●	●	○
Korea		●	●	◑	●	●	◑	●	●	●	●	●

Jurisdiction		Does the HTA process promote equity?				Engagement in the HTA process?						
		Geographic	Socio-economic	Other	For specific technologies	Patients and patient organisations	Members of the public	Industry	Clinicians	Academia	Other	For specific technologies
Norway		○	○	○	◑	○	◑	●	○	○	●	●
Poland		○	○	○	○	○	●	◑	○	○	●	○
Singapore		○	○	●	○	●	◑	●	●	●	●	●
Spain		○	○	◑	○	○	○	◑	●	○	○	○
Sweden		○	○	●	○	●	○	○	●	○	●	○
Switzerland		○	○	○	○	●	◑	●	●	○	●	○
Taiwan, Republic of China		●	●	●	○	●	○	○	●	○	○	○
The Netherlands		○	○	●	●	◑	◑	◑	◑	●	◑	●
United Kingdom	Wales	●	○	●	○	●	●	●	●	●	●	○
	Scotland	○	○	●	●	●	●	●	●	○	●	●
	NICE/NIHR (national)	●	●	●	●	●	●	●	●	●	●	●
USA		○	○	●	●	●	●	●	●	●	●	○
Yes & Partially		**10**	**9**	**22**	**11**	**21**	**20**	**23**	**22**	**17**	**23**	**13**
Not reported and No		**17**	**18**	**5**	**16**	**6**	**7**	**4**	**5**	**10**	**4**	**14**

CADTH = Canadian Agency for Drugs and Technologies in Health. INESSS = Institut national d'excellence en santé et en services sociaux. HQO = Health Quality Ontario. IHE = Institute of Health Economics. NICE = National Institute for Health and Care Excellence. NIHR = National Institute for Health and Care Research.

● Yes ◑ Partial ● No ○ Not reported/No information found.

Stand-out performers

The UK's NICE achieved a 'clean sweep' across all equity and stakeholder engagement categories charted in Table 6, with a 'yes' in each column. Belgium was close behind, with a single 'partially' instead of a 'yes' (although Belgium has only recently begun working with patient groups). Third was Canada's CADTH, with a 'not reported' in one column. Australia performed well but published sources did not report whether Australia's HTA process promotes equity or stakeholder engagement along special pathways, nor did they clearly articulate engagement with academia (noting, of course, that most of the health technology assessments done for government and performed by academic groups).

Japan and Korea stood out in terms of 'no' cells in Table 6, with there being evidence that Japan and Korea do not promote equity or (in Japan's case) patient engagement, although this is partly a function of scholarly work sufficiently attending to these jurisdictions to flag these issues.

Patterns and outliers in equity

In most jurisdictions, equity is somewhat promoted, in that some mention is made of equity being a consideration (especially in appraisal decision making). Australia, Austria, Finland, France, Taiwan, and the UK were clearest in articulating a concern for equity that spanned geographic, socio-economic and other inequities. All other jurisdictions showed gaps in not reporting a concern for one or more of those equity categories. Italy, Norway, Poland, and Switzerland did not report concern for any of those equity categories, while evidence suggested that Japan does not promote equity.

Equity seemed to be regarded as something in need of protecting, in that unjust inequalities should be reduced or at least not introduced or compounded when choosing whether to fund a technology. Alternatively, equity was regarded as something in light of which the true value of a health technology might be higher (rarely lower) than indicated by economic evaluation.

'Equity of access' was a recurring concept, implicitly referring to the right of groups or individuals to access health care without undue impediment in terms of out-of-pocket costs or any other factors. 'Unmet clinical need' was another recurring concept, though never defined. The implied notion was one of a group or individual with illness, and thereby in need of a health technology, but that technology had not yet been provided, including because nothing beneficial had yet been innovated. Japan was mindful of conditions with 'insufficient treatment' options. Concern was sometimes expressed for patients "most in need" or with "vulnerability" (Korea [79]), without elaborating on these concepts. NICE refers to people "most disadvantaged" and commendably substantiates this concept by giving regard to inequalities owing to geographic and socio-economic factors and "the circumstances of certain groups of people, such as looked-after children and people who are homeless" [80]. This may be partly due to NICE's social care

remit. Belgium refers to "at-risk groups" [81]. It is worth noting that while health benefits have been extensively considered and measured over recent decades, especially within the field of health economics, clinical need has received less scholarly attention [82].

Very occasionally equity was tied to justice, autonomy, integrity, solidarity, diversity, inclusion, and sustainability - although it was not clear whether this meant financial or environmental sustainability. For instance, CADTH expressed a commitment to post-market medicine evaluation that includes analyses sensitive to sex, gender and First Nations, in view of diversity problems in pre-market research. CADTH recognises that the primary evidence base itself can pose problems in terms of equity by creating a picture that is not truly reflective of the technology's effects in a real and diverse population, with the effect being that groups excluded from the primary research can be worse served by the technology once it is implemented. It is noteworthy that CADTH was the only jurisdiction of those studied to expressly discuss First Nations people [83]. Looking further afield, there is evidence that the National Health Council in New Zealand has considered "equity for the Maori people": In one report, the main question raised was: "How will a national procedure avoid aggravating existing inequality for the Maori people?" [84]. New Zealand's national HTA agency, the Pharmaceutical Management Agency (Pharmac), also "considers inequitable outcomes for Māori unfair and unjust, and also avoidable, and is actively working to eliminate them" [85].

Equity was sometimes mentioned in relation to specific types of technologies, including cancer medicines and precision medicine (CADTH), although it was not expressly stated why these technologies warrant special regard on equity grounds. NICE established the Highly Specialised Technologies Programme specifically to achieve "more equitable treatment access for very small populations with very rare diseases" [86]. Other jurisdictions, like Japan, also mentioned rare diseases in connection with equity. Presumably such populations warrant special regard (including in the form of a more accommodating ICER threshold [87]) because they miss out on efficiencies in medicines development, production and sale that are elsewhere gained through economies of scale. The only express argumentation to this effect was offered in a Belgian policy paper: "orphan drugs are considered differently from other drugs for reasons of absence of economical viability under normal market conditions" [88]. Norway is mindful not to define very small patient groups with rare conditions too broadly to keep its special pathway on track in the service of equity. Researchers have found that appraisal decision-guiding criteria mostly do not change when moving to rare diseases in Australia, France, Germany, Italy, Spain (Catalonia), Sweden, the Netherlands, New Zealand, England, Scotland, and Wales [89]. Spain and NICE did also consider "innovativeness" without explicitly defining this, although the notion seemed to combine "concepts of unmet need with [an] 'indisputable' therapeutic advance that alters the course of the disease" [89] (see also [90]).

Examples of other equity factors included the following.

- *Health status*. Severity was often identified with clinical need and given some degree of priority. That is, a technology that helped sicker people or people with co-morbidity (e.g., chronic disease, an inability to have surgery, or disability) was seen to have greater value, namely in a way not reducible to QALY gains. This may reflect some version of prioritising the worst off (Prioritarianism) [82].
- *Age*. Very occasionally, children (Japan), women of reproductive age [79], and older people (Taiwan) were given some degree of priority. On the other hand, Irish guidelines noted with caution the UK public attributing lower value to "improvements in health for the elderly and … those perceived to have contributed to their own ill health" [91]. At times, age was mentioned as something that should be considered on equity grounds, while at other times age was mentioned as something that appraisal decision making should occur *independent* of, say in accord with legislation aimed at preventing age-based discrimination. Regard for older people, for instance, appeared to go in three different directions: older age counts in favour of a person (being in greater need); or is regarded as irrelevant and discriminatory to consider; or counts against a person via reference to age-based normal health [92] or studied as public preferences in favour of younger people. Confusion or at least disagreement evidently abounds on the relevance of patient age in HTA decision-making.
- *End of life*. There was some discussion as to whether technologies that help at the end of life should be prioritised [90]. Sometimes this was discussed under the banner of the 'rule of rescue'. Australia gives some scope to the 'rule of rescue' without defining it. But how this concept is defined can potentially shape whether one looks upon it favourably. For instance, NICE states that it relies on the ICER and recognises that this reliance involves rejecting the rule of rescue, which NICE refers to as "the desire to help an identifiable person whose life is in danger no matter how much it costs" [80]. This definition is potentially loaded against the concept. An alternative definition is "the imperative to rescue identifiable individuals facing avoidable death, without giving too much thought to the opportunity cost of doing so" [93]. Whether the 'imperative' is characterised as psychological, moral or both then has bearing on the importance and potential role of the concept.
- *Other.* Very occasionally, there were further proposals: to consider different impacts for people based on their employment status, education or cultural background; to prioritise technologies that helped caregivers [94] or people with dependents (Ireland); and to consider how the technology stood to impact on future generations [79] or on "social cohesion, ease of suffering, impact on personal relationships, impact on safety and security [from violence], respect and dignity" [95].

Researchers have developed a framework for systematically considering ethics and equity when forming recommendations for vaccine programmes [96]. The framework equates to something of a checklist or series of questions aimed at ensuring that proper

consideration is given to the vaccine programme upholding ideals of respect for persons and communities, beneficence and non-maleficence, justice, trust, and the procedural aspects of accountability, inclusiveness, responsibility, responsiveness and transparency [96]. The framework also commends examining any possible equity problems relating to a person's pre-existing condition, place of residence (e.g., nursing home), race/ethnicity/culture/language/immigration-or-refugee status, occupation, gender identity/sex, religion/belief system, education/literacy level, socioeconomic status (including income), social capital (including support networks), age, and other factors (such as risk behaviours) [96].

Industry was sometimes invited to comment on equity in its submissions (e.g., Australia and Denmark). There were no data on how frequently industry took up the invitation, though there were some data on the prevalence of equity consideration in appraisal decision making. One report suggested that equity considerations or 'social value judgements' (SVJ) are more commonly considered in decision making for medicines (n=304) than medical devices (n=67) [97]. The report found that very few HTA bodies reveal their SVJs in their guidelines, even while they do consider them, "albeit not in a consistent manner" [97]. For medicines, the most common SVJ concerned quality-of-life improvement for patients and carers (27%) and "unmet need in specific disease areas" along with innovation (11%) [97]. SVJs usually (82%) *favoured* the technology under review [97].

Patient engagement was often viewed as serving or enhancing equity or as required on the basis of equity (Belgium). Engagement with patients from diverse backgrounds was also commended to help identify diverse equity concerns.

Patterns and outliers in stakeholder engagement

Stakeholder engagement occasionally features as an over-arching guiding principle of an HTA organisation (France's HAS and Canada's CADTH and IHE). In Latin America, stakeholder engagement is limited but there is agreement on its importance for HTA's legitimacy and for the protection of "decision makers from potentially distorting external influences" [98].

Appraisal committees can include:

- clinicians
- health economists
- patient representatives
- members of the public ('lay')
- ethicists
- managers
- academics
- government agency staff (in an advisory role)
- government and professional association representatives
- industry representatives

There is some interest in multi-stakeholder engagement processes, particularly around specialised technologies of the kind that can occasion special HTA pathways. Specialised technologies or contexts (such as orphan drugs or real-world evidence) tend to occasion concerted efforts at stakeholder engagement. In disinvestment, stakeholder engagement (e.g., via special committee) has even been described as the single most important element [99]. Post-market evaluation occasions concerted engagement with industry and clinicians.

Industry

Industry was commonly engaged by being permitted or invited to provide a submission for funding, although additional modes of industry engagement included:

- offering an advisory service to industry for a fee, on matters of science and patient engagement (the UK's NICE) [100]. There has been a call for HTA agencies to define the early advisory services that they could offer industry [101].
- early dialogue [102], presumably about regulatory or funding hurdles and associated evidentiary requirements. Early dialogue among multiple stakeholders is thought to be especially important with specialised technologies, e.g., innovative cancer medicines [102].
- inviting industry to respond to the HTA report, including at more than one time-point. In Scotland and Europe, industry has been given the opportunity "to comment on the factual accuracy of what is said about their product" by competitors in their submissions [103, 104].
- inviting industry to present for 10 minutes in the appraisal committee meeting. Australia's PBAC found 45% of these presentations "informative or moderately informative" and 18% "uninformative" [105].
- holding an additional meeting if funding is denied but the medicine is deemed to treat "a serious, disabling, or life-threatening condition with no other treatment option", presumably to resume price negotiation or explore alternate funding pathways [106].
- permitting industry to appeal against a funding decision or to request further independent review.
- permitting or inviting industry to re-submit old applications with new evidence or indications.

There is evidence that invitations for public comment on assessment reports mostly occasion industry comments on method [107]. Perhaps for this reason, some jurisdictions (e.g., France, Germany, New Zealand, the Netherlands, and Wales) limit online calls for comment to patient groups [89].

Clinicians

The involvement of 'experts' was commonly cited as essential in obtaining the best available evidence, though the nature of the expertise required was not always spelled out. Clinical experts and experts in particular disease areas or scientific methodologies were commonly engaged. Clinician engagement is regarded as especially important as intervention complexity and innovation in health technologies increases. It has been used to guide the prioritisation of technologies for assessment in Spain and the US. Health care providers and "other health system stakeholders" are also often engaged [108].

Patients

Patient engagement is regarded as especially important where clinical knowledge is limited (for instance, with rare diseases or innovative technologies). Typically, the implied primary rationale for patient and other stakeholder engagement is the instrumental or technocratic goal of *enhancing the evidence base*, as distinct from the substantive or democratic goal of giving affected parties their say. Belgium and NICE, as engagement leaders, did appear concerned to engage patients for "procedural" reasons as well as to enhance evidence [109-111]. HTA stakeholders agree on the instrumental goal of enhancing evidence and on the value of a formal process for gathering and integrating information from patient and public engagement, but they remain uncertain on how to best engage and how to best use the information obtained [112].

A 2014 systematic review found that patients were generally not given *direct* roles in reducing uncertainties relating to value for money, affordability or technology adoption or diffusion [113]. Instead, patients were involved in "activities aimed at generating information on clinical benefit", which then informed discussions on uncertainties [113]. Sweden and the US have engaged patients to prioritise research projects based on knowledge gaps important to patients [114, 115].

Jurisdictions such as Australia, Germany, Scotland, Singapore, and Wales have dedicated patient engagement staff, committees, or councils. Their roles include:

- assisting government to engage patients more effectively.
- presenting information about patient experiences to the appraisal committee
- informing policy
- increasing public understanding
- collecting new data on patient experiences through small-scale primary research (e.g., interviews and focus groups with patients and carers)
- enhancing methods of patient engagement
- mentoring patient representatives who sit on appraisal committees
- recruiting patients or patient organisations for data collection
- supporting patient organisations to provide comment.

Commendably, Denmark provides a guide for its patient representatives [116] and details its patient engagement methods, together with its view of what works well [117]. Expert opinion suggests that the UK's NICE, Canada's CADTH and Scotland's SMC do likewise.

Methods for collecting data on patient perspectives included:

- canvassing or formally reviewing published literature
- personal consultation (presumably a small meeting) [118]
- inviting a small number of patients (e.g., five) to test some texts for their content and readability [119]
- opening public consultation
- conducting appraisal meetings online to facilitate the attendance of patient members (especially during COVID-19) (Taiwan and the UK's NICE). In the UK, this online engagement was felt to be more accessible and inclusive but also restrictive of opportunities to form interpersonal relationships, bounce ideas and gauge people's reactions [120].
- conducting original qualitative research with patients with "lived experience" of the technology, along with their "families and other caregivers", as routinely occurs in Ontario, Canada [121]. In Germany, an external contractor conducts focus groups and interviews with patients [119]. In Spain, methods have included patient surveys.

Europe has mostly engaged patients via online forms and one-on-one conversations [104], together with group conversations and scoping meetings [122]. Internationally, patients are mostly engaged through public consultation and direct involvement is less common [123]. The window of opportunity for patient input is often small, e.g., several days or weeks before and after the assessment report is finished and shared.

Patient recruitment methods span:

- the use of patient advocacy networks, including direct outreach to them
- outreach to patients identified in news articles, social media and the health service.
- inviting patient feedback or committee members via websites and social media
- symposia and conferences
- introduction by clinicians

Exemplars in engagement (CADTH and the UK's NICE) profess to use information from patients in all phases of HTA, including in protocol development and throughout the fuller assessment and appraisal. NICE provides a flowchart of patient involvement at every stage [124] (see Figure 12). Patient engagement in primary evidence development and HTA scoping or topic development [125] have also been tried.

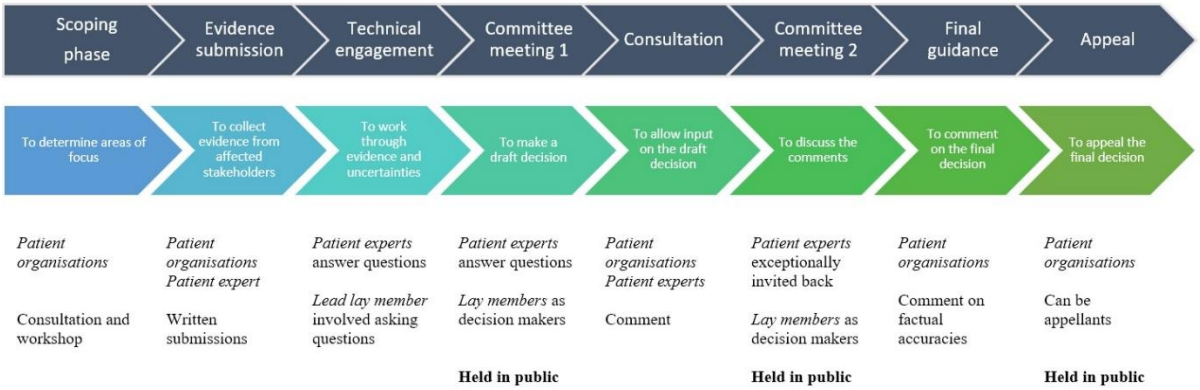


Figure 12 NICE Patient Engagement. Adapted from [124]

However, problems with patient engagement, despite demonstrated commitments to it, have included:

- sporadic and unsystematic engagement (Austria)
- challenges with recruitment, capacity building [126] and timeliness [122]
- disagreement and uncertainty on the role and impact of public and patient engagement [112] (see also [122, 127])
- differences in philosophy and priority given to public and patient engagement, including an emphasis on evidence-based principles which functions to exclude the meaningful integration of patient input [127] (see also [112])

To help with the last two, researchers have recommended that conflicts "between multiple epistemic traditions" be openly acknowledged [127] (see also [128]). To help with recruitment, it has been suggested that a register or pool of relevant patients or patient organisations be created and used for making contact [122].

Patient groups commonly report problems in:

- recruiting patients [129]
- knowing the impact of their contributions [111, 129], despite commitments to transparency
- having enough resources to prepare submissions (potentially leaving patient groups reliant on industry or vulnerable to problematic influence from industry).

Researchers have suggested that "the lack of clear reporting on the use of patient group input in deliberations and therefore accountability to patient groups limits progress in patient involvement in HTA" [130]. A clearer view of how patient inputs are used will give patients clearer guidance on the kind of information to provide [130]. Adequately resourcing patient engagement (e.g., with government funds or through cost recovery with industry) stands as a potential means of reducing the possibility of problematic influence from industry on patient groups. The UK's NICE has a Public Involvement Programme to promote the involvement of patients, families, carers, and the public "regardless of disability, language, or other potential barriers" [80]. Presumably supports are resourced and offered so potential barriers do not prevent engagement.

Concerns are repeatedly raised by patient groups about time and resource constraints. Proactive engagement strategies (e.g., the HTA agency conducting interviews) hold promise in this regard, in that they take the resource burden off the patient groups, being born instead by another stakeholder (the HTA agency, or government in funding the evaluation, or industry in providing submission fees). Proactive engagement strategies could also help to address a "lack of information" on the part of patients and the public about HTA and a "lack of guidance and policies to support" their engagement, which were identified in a global systematic review [123].

There are some data on the frequency of patient submissions in HTA. Researchers found that in 2017-2018 France's HAS received 79 contributions from 44 patient groups for 78 of the 592 HTAs (only 13%), with almost double (25%) of the medicine HTAs receiving one or more contributions. The contributions covered "quality-of-life aspects, access to care, and personal and family impact" [131]. The patient groups varied greatly in size and budget and were constrained by time and human resources [131]. In Taiwan in 2015-2020, 30 patient insights were published (19 relating to oncology) but challenges remain around timeliness, resources and visibility of the patient inputs [132]. Researchers found 119 patient insights in 30 consecutive drug assessments performed by the CADTH Canadian Drug Expert Committee (CDEC) [133]. Of those 119, "89 were included in assessment protocols; 61 in reported clinical trial data; and 67 insights were reflected upon within the CDEC Recommendations", showing that patient insights "are used by CADTH reviewers to frame an assessment and used by CDEC to interpret the evidence" [133].

A 2021 study assessed the impact of patient input to highly specialised technologies (HSTs) and interventional procedures (IPs) guidance at the UK's NICE [134]. Researchers found that patient input had more impact for HSTs. Specifically, for IPs, 35% of respondents stated that patient input had no impact, whereas no respondents stated this for HSTs. Respondents most commonly felt that patient input provided new evidence and helped to interpret other evidence. While patient input did not necessarily change recommendations in an explicit way, it nonetheless provided "context, reassurance, and new information to the committee" [134].

Expert opinion suggests the following: HTA agencies like Sweden's SBU, Canada's CADTH, Scotland's SHTG, and Wales's HTW do qualitative evidence synthesis or rapid qualitative evidence synthesis. Robust methods such as these produce outputs that are labelled and treated differently to the products of participation. The former outputs comprise patient-based evidence, and the latter outputs comprise patient input or insights. The former can be critically assessed, and the latter can be responsive to local issues and dynamic. Drawing a distinction between the two is important because (expert opinion suggests) this is where HTA bodies can get confused about how to use outputs. (Patient-preference studies represent another type of patient-based evidence.)

Expert opinion further suggests that judgements about patient engagement really concern *who* to engage (e.g., patients, patient experts, patient organisations), *when* to

engage (e.g., early or at appraisal), *how* to engage (e.g., via written submissions or dialogue), then how to integrate the information obtained and what patient-based evidence should be used to complement this. The Patient and Citizen Involvement Interest Group (PCIG) of HTA International (HTAi) is currently undertaking a "review of current methods and processes for patient involvement in Europe", but findings are not yet available [135].

EUnetHTA's HTA Core Model 3.0 was developed to guide HTA [136]. 'Patient and social aspects' constitute a core domain of the model: "Patients, caregivers and individuals will have a range of perspectives and an HTA should seek to gather as much evidence as possible to understand these wide ranging views" [136]. Expert opinion suggests the Core Model was used in a variety of European countries, as well as in joint actions.

Terms like 'patient' are often used differently. For instance, the HTA Glossary defines a patient as "A person, presenting with clinical signs or not, who consults a physician" [1], whereas others regard a patient as "anyone who has direct experience of living with the condition being studied in the HTA or who may be eligible to receive the technology (e.g. specific members of the public who might be invited for vaccination or to undertake a diagnostic intervention)" [137]. The latter group has elsewhere been conceptualised as a 'consumer' or service 'user' but *not* a patient, say in so far lacking disease or specific engagement with the health service [138]. Researchers have proposed to reduced unwarranted variation in terminology by defining a patient as "An individual with a disease or disorder who is using some aspect(s) of the healthcare system because of this disease or disorder", where members of the public, consumers/users, carers/caregivers, lay people, patient advocates, and so on are each defined differently, especially because of the diverse interests they can have in relation to a given HTA [138]. Engagement activities may focus on patients, as just defined, or a different group, as follows.

- Consumer/user. "An individual who uses, has used, or intends to use a particular health technology or service" [138].
- Carer/caregiver. "An individual who is the unpaid informal primary or secondary caregiver for a patient" [138].
- Patient advocate. "An individual who represents and advocates for the interests of a particular group of patients on a committee" [138].
- Patient member. "An individual who has been selected to support the inclusion of the interests of patients in Health Technology Assessment processes on a committee" [138].
- Consumer member. "An individual who has been selected to support the inclusion of the interests of consumers on a committee" [138].

The public

The distinct interest of members of the public (say, as taxpayers or stewards of a good society and sustainable health system) were only very occasionally differentiated from

the interests of patients, carers and their representatives (say, as people wanting the best possible health care for themselves and those close to them). For instance, Denmark's HTA Handbook frequently mentions "citizens", but confusingly this often refers to "patients as citizens" [139]. One research study suggests that patient and public member positions "may have been created without a good deal of consideration for the different contributions they could make", but many in HTA now see a distinction [112]. Researchers have proposed an updated taxonomy of patient and public groups, emphasising how they can be conceptually distinguished by their different and sometimes divergent interests [138]. Ireland distinguishes patients from the public but considers only patients as stakeholders, in that stakeholders are expressly regarded as "distinct from the general public" by stakeholders having "a direct interest in the process and outcomes" of an HTA, with the imputation that the general public has, at most, an indirect interest [140].

Modes of engaging the general public have included:

- the online publishing of policies, procedures, analyses, decisions, meeting summaries, or full assessment reports (there appears to be wide variation internationally in the extent of what is made public)
- establishing and running a Layperson Advisory Committee [141] or Citizen Committee for Participation (Korea) to help make funding or other recommendations
- conducting appraisal meetings in public. Since its establishment in 2002, the UK's All Wales Medicines Strategy Group has met in public (with members of the public able to attend and view deliberations). The Scottish Medicines Consortium, the USA's Advisory Committee on Immunisation Practices (ACIP), and the USA's Institute for Clinical and Economic Review's (ICER) also hold their meetings in public.

This paper's findings on transparency of the HTA process should also be considered as a potential aspect of public engagement.

There was even evidence of actively avoiding public engagement. For instance, there is research evidence that Finnish authorities "do not engage in public discussion about ongoing processes" because they feel that such engagement is made impossible by campaigns "inappropriately" pressuring them to fund some medicines [142].

The under-emphasis on public engagement in the HTA literature was notable. Public engagement was often implicitly reduced to a matter of transparency and public accountability, whereas the potential scope for public engagement is much larger (e.g., gathering data on public funding priorities and the public's willingness to pay for technologies or particular aspects).

Academia

Ethicists are occasionally engaged as committee members or, along with legal experts, as experts for specific technologies or technology types (e.g., whole-genome sequencing or orphan drugs). Dutch academics, in particular, have conducted many research projects into HTA methodology [92], presumably because of a dedicated research funding stream.

HTA PATHWAYS FOR SPECIFIC TECHNOLOGIES AND POPULATIONS

In this section, different specialised HTA processes and pathways are discussed for reimbursement of different technologies such as high-cost medicines, medicines for high unmet clinical need but uncertain long-term effects, antimicrobials, non-sponsor submissions and medicines for rare diseases (Table 7). Overall, the findings indicate that most countries reimburse special technologies through managed access schemes for a specified period, conditional on evidence development and a subsequent reassessment.

One of the main challenges identified in the assessment of special technologies is that the evidence base indicated uncertain clinical effectiveness and cost-effectiveness. Mostly of the medicines eligible for these pathways are for the treatment of severe and highly debilitating conditions. We found that three countries (France, the Netherland, and Germany) exempt medicines from HTA assessment if there is high unmet clinical need, such as for rare disease. The medicines are assessed for added therapeutic benefit in each of these countries and due to the high unmet clinical need, the added benefit is considered proven. We did not find any study that discussed the potential risks of this approach.

As mentioned above, evidence for clinical effectiveness and cost-effectiveness is usually scarce for these medicines due to the small patient populations. Therefore, some countries, namely Canada and UK, allow flexibility in the evidence requirements and decision-making threshold for high-cost medicines, medicines for conditions with high unmet clinical need (such as rare disease) and uncertain long-term effects. For instance, in the UK, such medicines may be reimbursed through specialised funds even with a higher ICER threshold. Each specific technology is discussed further below:

Table 7 Pathways for different/specific technologies

Jurisdiction		Is there a separate pathway for…?							
		First-in-class/ first-in-indication technologies	*New, high-cost technologies*	*Populations with high unmet need*	*Technologies with uncertain or long-term outcomes*	*Co-dependent technologies*	*Anti-microbials*	*Technologies without a sponsor*	*Rare diseases*
Australia		◑	●	●	●	●	●	○	●
Austria		○	●	○	○	○	●	○	●
Belgium		●	●	◑	○	●	○	○	●
Canada	CADTH (national HTA agency)	◑	●	●	●	●	●	●	●
	INESSS (Quebec)	○	○	○	○	○	○	○	○
	Ontario (HQ)	Follow CADTH Advice							
	IHE (Alberta)								
Denmark		○	●	○	○	○	○	○	●
Finland		◑	○	◑	○	●	●	●	●
France		◑	●	●	●	●	◑	○	●
Germany		○	●	○	●	●	◑	○	●
Ireland		●	◑	◑	●	●	●	●	●
Italy		◑	◑	●	○	○	○	○	●
Japan		●	●	●	●	●	●	●	●
Norway		●	●	●	○	○	●	○	●

Jurisdiction		Is there a separate pathway for…?							
		First-in-class/ first-in-indication technologies	***New, high-cost technologies***	***Populations with high unmet need***	***Technologies with uncertain or long-term outcomes***	***Co-dependent technologies***	***Anti-microbials***	***Technologies without a sponsor***	***Rare diseases***
Poland		○	○	○	○	●	●	○	●
Singapore		◑	◑	●	●	●	○	○	●
South Korea		●	◑	●	●	○	○	○	○
Spain		●	◑	●	○	○	●	●	○
Sweden		●	●	●	●	○	◑	●	○
Switzerland		○	○	○	○	○	○	○	○
Taiwan, Republic of China		○	◑	○	●	○	○	○	●
The Netherlands		◑	●	○	○	●	○	○	●
United Kingdom	Wales	Follows NICE Advice							
	Scotland	●	●	●	●	○	●	○	●
	NICE/NIHR	○	●	●	●	●	◑	○	●
USA		■	●	●	●	●	●	◑	○

CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Pathways for first-in class, high-cost, uncertain long-term effects and for population with high unmet clinical need

These technologies have been grouped as similar approaches to reimbursement were observed in different countries:

Australia

In Australia, technologies such as first-in class, high-cost technologies targeting high unmet clinical need, and technologies with uncertain long-term effects are usually reimbursed using managed entry or access agreements (MEAs) such as CED. These HTAs go through the normal PBAC evaluation and appraisal process but if the medicine or technology is rejected but meets certain criteria, an MEA may be considered. The resubmission must provide a section dedicated to the additional evidence that would be gathered [143]. In some cases, PBAC may nominate an early re-entry pathway for resubmissions it considers that the uncertainty can be easily resolved, or if new clinical evidence is not necessary to support any new clinical claim in the resubmission or a revised economic model is not necessary to support economic claims in the resubmission [45].

The Life Saving Drugs Program (LSDP) provides access to essential and high-cost drugs for eligible patients with rare and life-threatening diseases. For inclusion on the LSDP, the submission must first be considered by PBAC. The PBAC should accept the clinical effectiveness of the submitted drug but reject it from inclusion on the PBS due to uncertain or poor cost-effectiveness. After the PBAC outcome, all the submissions seeking funding through the LSDP are considered by the LSDP Expert Panel. The sponsors can submit a response to the advice provided by the Expert Panel. The Chief Medical Officer (CMO) will make a final recommendation to the Minister regarding funding through the LSDP. All the medicines listed on the LSDP undergo post-market review for usage and financial costs after 24 months to ensure the performance and use of the medicine fulfills the listing conditions and expectations[144].

Other Jurisdictions

I. Managed Access agreements

For special technologies such as high-cost medicines, first-in class and medicines for populations with high unmet needs such as rare disease and with uncertain evidence, many jurisdictions mentioned reimbursing at least one of these technologies through managed access schemes i.e., Austria, Belgium Canada, France, Finland, Germany, Italy, Ireland, Spain, South Korea, UK (England, Wales and Scotland) and USA). The definition of some concepts such as ‘rare diseases’ varies across different jurisdiction. Challenges are commonly reported with assessment across these agencies, mainly due to uncertain clinical effectiveness and cost effectiveness due to the small patient population. Similarly, the high unmet clinical need is loosely defined with some countries defining

it as a treatment for serious and highly debilitating disease with no available alternative medicines, while in other countries no consistent definition exists. Moreover, we noticed that the details and nature of managed access agreements are confidential, therefore, it was not possible to establish if there are any similarities or differences across different jurisdictions.

NICE (England and Wales) and SMC (Scotland), recommend listing of high budget impact treatments for populations with high unmet need through patient access schemes, commercial access agreements (laying out commercial terms for NHS funding) and flexible pricing [27, 145]. The purpose of these agreements is to mitigate any uncertainty during funded access.

Similar trends were observed in Belgium, Canada, France, Finland, Italy, Singapore, South Korea, UK, and USA. In Belgium, medicines are eligible for managed entry agreements if there is added therapeutic benefit or value, of if the medicine is indicated for a small population (e.g., orphan drugs), or for severe indications with no alternative treatment, or where the comparator is also under a managed entry agreement [146]. There is also an early temporary reimbursement pathway for early access to medicines for treating conditions with high unmet clinical need.

Applying similar criteria in South Korea, the medicines for population with high unmet clinical need can be reimbursed through three pathways: 1) Essential drugs, 2) Risk sharing arrangements (RSAs), and 3) Pharmacoeconomic evaluation (PE) exemption (exemption of economic evaluation) [147]. If a drug was designated as essential drug, the cost-effectiveness evaluation can be waived and the price is set according to the price listed in reference countries (UK, Italy, France, Germany, Switzerland, the US, and Japan) [148]. The criterion of an essential drug is like the rule of rescue in Australia (a) it has no alternatives (including alternative drugs and treatment methods); (b) it is used for treating serious life-threatening conditions; (c) it is used to treat small patient groups, such as those with rare diseases; and (d) it demonstrates a significant improvement in clinical efficacy or survival [148]. Up until 2019, 10 drugs were reimbursed under this pathway [148]. The medicines which treat serious, life-threatening conditions with no alternative treatment can also be listed with a RSA for up to 4 years, subject to re-evaluation to maintain the listing status [149]. PE exemption allows access to medicines that do not meet the criteria of RSA. The manufacturers share risk with NHI under this scheme in the form of an expenditure cap [149].

Also in Italy, an innovativeness- based assessment framework was introduced in 2017 to ensure easier and faster access to the market for innovative drugs. Under this framework, innovative drugs which fulfill high unmet clinical need but are associated with high budget impact or uncertain evidence can be approved conditionally in order to manage budget impact, address uncertainty in clinical and/or cost-effectiveness evidence and optimise performance. However, due to the decentralisation of market access and regions responsible for allocation of budgets for health care services in Spain

and Italy, there may be additional agreements with regional authorities for access to regional markets [150].

II. Coverage with Evidence Development

One of the most common forms of managed access agreements observed in our dataset for special technologies is coverage with evidence development (CED) agreements. Medicines with uncertain clinical effectiveness specifically concerning long-term effects are getting reimbursed in many countries with CED agreements. Under these agreements, the payer/s agrees to reimburse a specific medicine for a specific period due to clinical need but with certain conditions attached. These conditions are usually related to the collection of additional evidence or real-world data to better understand the treatment's outcomes and impact on patients. We observed that in most countries, CED agreements often apply to specific patient populations who may have limited treatment options or for whom the evidence supporting the efficacy of the treatment is still evolving. The agreements usually outline specific timelines and milestones for data collection and analysis. Based on the results of the data collection and analysis, the payer/s re-evaluates the coverage decision. If the additional evidence confirms the treatment's effectiveness and safety, the conditional coverage may transition to full coverage without the need for further data collection. On the other hand, if the evidence raises concerns about the treatment's value or safety, the payer may reconsider coverage or negotiate further conditions.

In the USA, the Centers for Medicare & Medicaid Services (CMS) operates a Coverage with Evidence Development (CED) program. This initiative is used to provide Medicare coverage for certain medical interventions that are promising but require additional evidence to determine their effectiveness. Through this program, Medicare may cover treatments on the condition that data is collected on patient outcomes and other relevant measures. The medicines covered under Medicare Plan D can have conditional coverage or limited coverage depending upon the availability of evidence or budget impact. As per CED requirements, the sponsors are required to provide the results of the clinical trials within 12 months through publicly available registry or peer-reviewed publication. Medicaid coverage policies limit the state’s authority to limit or negotiate rebates with manufacturers specifically for high-cost treatment which mostly get market approval through FDA expedited pathways. The states are required to provide coverage for all the drugs approved by FDA and which are included in the MDRP [151]

In Canada, the pan-Canadian Oncology Drug Review (pCODR) and CADTH may recommend conditional reimbursement for cancer medicines. The sponsors are then required to conduct post-market studies to gather more evidence on the medicine's effectiveness. CADTH can consider non-randomised trials and RWE in resubmissions. Individual medicine plans at regional (provincial and territory level can execute a price listing agreement (PLA) (including CED) after the letter of intent is finalised by the pan-Canadian Pharmaceutical Alliance (pCPA) for such submissions. However, the use of a PLA is very inconsistent across different provinces with only Alberta having a well-

developed PLA program to inform the parameters of agreement. Similarly, Ontario has implemented an Evidence Building Program (EBP) to inform the CED agreements and provide guidance to sponsors for evidence development [152]. For other provinces, there is no consistent implementation of PLA for medicines with uncertain long-term effects. Additionally, medicines approved by Health Canada for the treatment of a rare disease must fulfill certain criteria, such as it must be life-threatening and seriously debilitating, with an incidence of fewer than 5 in 10,000 people affected, but typically closer to 1 in 100,000, leads to a reduced lifespan, be associated with high burden for caregivers and be difficult to study due to the size of the patient population. The CADTH drug review committee may recommend reimbursing such drugs via CED due to the significant unmet clinical need [49].

In Germany, G-BA can proceed to specific CED agreements with the pharmaceutical company usually referred to as time-limited resolutions (TLR) agreements. A study indicated that only in 2017, 29% of medicines assessed were subject to TLRs with an average of 2.5 years until resolution [153].

The NHS (UK) offers special managed access funds for innovative medicines which require further data to resolve uncertainty. Two such funds, namely the Innovative Medicines Fund (for noncancer drugs) and Cancer Drug Fund, provide an opportunity for patients to access innovative medicines whilst data are being collected, specifically for seriously debilitating and severe diseases for which there is no alternative treatment available. However, medicines will only be recommended by NICE for managed access if they demonstrate plausible cost-effectiveness and are priced reasonably during the period of managed access. In Scotland, the SMC allows interim acceptance of innovative medicines. Interim acceptance means that medicines are accepted for use, subject to reassessment when further evidence is available. The period of interim acceptance is dependent on the conditional market authorisation status provided by the MHRA. When MHRA converts conditional market authorisation to full market authorisation, the sponsor needs to provide an updated submission to SMC for reassessment [61]. One example of CED agreements in Scotland is for medicines for ultra-rare diseases (defined as prevalence of 1 in 50,000 or less in Scotland). Sponsors are required to apply for initial assessment to SMC within two years after the validation of an ultra-orphan medicine. After the initial assessment, access is granted up to three years subject to further evidence development. After this temporary access period, if no updated evidence is provided, the SMC will remove the recommendation advice. The initial assessment by SMC highlights the uncertainties in the evidence that will inform the data collection stage of the ultra-orphan pathway. The appraisal process considers the nature of the disease, clinical impact, value for money and cost to the NHS. A similar approach is also followed in Belgium, where medicines for rare disease can be reimbursed for 1 - 3 years with the requirement of further evidence development. The decision to continue the reimbursement is based on evidence submitted in a resubmission [154].

In the Netherlands, medicines developed for conditions associated with high unmet clinical need can be conditionally listed for reimbursement with a CED agreement [155]. To be eligible for conditional listing (CL), the medicine should fulfill an EMA definition of unmet medical need [156] and must be conditionally approved by the EMA in one of three categories: 1) approval with orphan disease designation [157], or 2) conditional market authorisation [158], or 3) market authorisation under exceptional circumstances [159]. The process of CL consists of three phases [155]:

- Phase 0: The conditional inclusion dossier may be submitted as an early submission before the HTA assessment by ZIN or after a negative recommendation from ZIN due to insufficient evidence. ZIN and the sponsor discuss the possibility of conditional inclusion and an early submission dossier during the scientific advice and pre-consultation stage.
- After the eligible medicines dossier for CL is submitted to ZIN, ZIN assesses on five criteria: 1) medicine should address a required EMA designation (orphan designations, conditional or exceptional approval), 2) fulfil unmet need (as defined by EMA), 3) sponsor should be the leading applicants of CL and other co-applicants should be declared, 4) data collected in the study should warrant inclusion of medicines in basic health care, and 5) the study should be finished in a timely manner (at most within 7 years). In some cases, a longer period may be necessary, though it may never be longer than 14 years.
- After ZIN confirms that all criteria are met, they will advise the Minister and provide any additional information that may inform the price negotiation process. Price negotiation and details of the CED agreement are discussed in this phase. A medicine can be conditionally listed only if ZIN provides a positive recommendation, and the Ministry of Health, Welfare and Sport agree on a price.

After CL approval, sponsors are required to provide progress reports and relevant interim findings annually. During this annual monitoring, ZIN assesses the progress of the project and advises the Minister whether to continue the study. The interim outcomes are pre-agreed. Six months prior to the end of the CL period, a final review will made by ZIN to advise the Minister whether the medicine should be included in the basic health care package.

III. Flexible Decision-making Thresholds

Along with managed access schemes, some countries allow a higher level of resource use and broader consideration of different treatment value aspects, such as clinical effectiveness, nature of the disease, impact beyond direct health benefits and value for money, when assessing innovative medicines specifically for rare diseases. The willingness-to-pay can vary on case-by-case basis based on equity and need for the medicine.

For countries where funding and provision of care services is delegated to regional/provincial governments, such as in Canada, Italy, Spain, and Sweden, the unequal distribution of need for Advanced Therapeutic Medicinal Products (ATMPs) across different regions poses a funding challenge at a regional level, specifically for

smaller regions with a limited budget. In Sweden, TLV is working on developing payment models for high -cost treatments that can balance innovation with cost control [160].

NICE allows flexibility in the decision-making thresholds on a case-by-case basis for high-cost medicines. The high-cost medicines or ATMPs can be assessed through two processes: the Single technology appraisal (STA) and the Highly Specialised Technology Programme (HSTP). The ATMPs undergoing the STA pathway usually target non-rare diseases and are assessed the same as any other medicine, with reliance on a cost-effectiveness analysis. The HSTP usually targets ultra-rare diseases (defined as 1:50,000 population in England) and is appraised under the Highly Specialised Technology evaluation (HST) process [161]. According to the technology appraisal guidelines, NICE typically has an ICER threshold of within £20,000–30,000 per QALY; however, ATMPs with ICERs of £30,000–50,000 were recommended for the Cancer Drug Fund (CDF). Three ATMPs were also recommended as HSTPs with ICERs of £100,000 per QALY [90, 162, 163]. Medicines that are eligible for survival criterion have also been recommended with ICERs higher than the conventional range.

In Norway, the HTA process is also adapted to consider higher willingness-to-pay for medicines for rare diseases. As indicated in the Norwegian Regulations on Medicinal Products ("legemiddelforskriften") §14-5 "For extremely severe conditions, a higher level of resource use in relation to the benefit will be accepted than for lesser severe conditions." The criteria for any medicine to be considered under this regulation is that it targets a very small population; fewer than approximately 1 patient per 100,000 population or fewer than approximately 50 patients in Norway [164].

IV. Price Negotiations

Two countries (Germany and the Netherlands) specifically mentioned price negotiations as a mechanism to allow access to high-cost medicines.

In Germany there is no special pathway for high-cost medicines, however, the price negotiation process that follows a G-BA decision on the added benefit allows SHI bodies and sponsors to negotiate different arrangements, such as discounts and rebates, to lower medicine prices for SHI bodies.

In the Netherlands, from 2015 a new set of rules were also introduced for high budget impact medicines, including first-in class or first-in indication. Any medicine expected to cost over EUR50,000 per patient per year with a budget impact of EUR10 m, or with an overall budget impact of EUR40 m or more per year, is placed under a 'lock system'. This implies that until financial and price negotiations occur, these high budget impact medicines are excluded from the basic insurance package. For all such medicines, an HTA assessment will be carried out to inform the negotiation process. The medicines are taken out of the lock system only after a negotiation agreement has been reached between the sponsor and VWS which allows reimbursement for eligible patients at a socially acceptable price. For instance, the first immuno-oncology products to market, such as Keytruda and Opdivo, were placed on lock system until negotiated agreement was reached [165, 166].

V. Exemption from HTA/Abbreviated HTA Process

In three jurisdictions (France, Germany, and the Netherlands), medicines designated as orphan drugs by the EMA are either exempted from traditional HTA or subject to an abbreviated process and added therapeutic value is considered proven. In these three countries, orphan drugs are made accessible to patients at a price set by the medicine sponsors and only subject to an abbreviated HTA process if its annual budget remains under EUR30 million (for France), EUR30 million (for Germany) or EUR2.5 million (for the Netherlands). If any drug exceeds this budgetary threshold, the medicine will go through a standard HTA process [89]. In Germany, the orphan drugs are assessed in-house by G-BA. While assessing additional therapeutic value, orphan drugs do not need to be compared to an appropriate comparator like other medicines as added benefit is always automatically assumed. The sponsors are required to submit an abbreviated dossier to the G-BA, meaning that all sections are not mandatory although the evidence requirements are same as other medicines. G-BA may only commission IQWiG to determine the size of the population and treatment costs whereas the determination of the likelihood and extent of added benefit is conducted in-house by G-BA [167, 168]. A recent study indicated that this approach has economic implications as orphan drugs are usually more expensive than normal drugs and automatic designation of superiority may be used to legitimise higher market prices. In Germany, automatic reimbursement of orphan drugs may not only put pressure on the health budget in Germany but may also result in higher prices in other EU countries due to external reference pricing. Of the 89 orphan drugs assessed in this study, and that later underwent standard HTA in Germany, 54% were found to have no added therapeutic value mainly due to the lack of robust evidence and comparison with the standard of care [169].

A new regulation, GKV-FinStG, introduced in Germany in 2022 reduced the annual revenue threshold for orphan drugs from EUR50 million to EUR30 million. In future, this may result in many orphan drugs undergoing reassessment and price negotiations [16].

A ‘lock’ system was piloted in 2015 in Netherlands and formalised into a law in 2018 by the VWS in response to fiscal pressure on hospital budgets. As mentioned earlier, orphan drugs historically were not assessed and automatically qualified for reimbursement on registration as hospital drugs. As a result, orphan drugs which enter the lock system based on the criteria mentioned above are now undergoing HTA to determine whether to reimburse them, during which time the medicine is not included in the health care benefit package.

Similarly, medicines for rare diseases are also exempted from cost-effectiveness analysis in Japan and South Korea. In South Korea, the price for medicines for rare diseases is determined based on the price listed in the reference countries (UK, Italy, France, Germany, Switzerland, the US, and Japan) [34].

VI. Real-World Evidence

There is also an increasing interest in utilising real-world data to supplement existing clinical evidence that may be uncertain. For instance, NICE (UK) and ZIN (the

Netherlands) mention that real-world evidence (RWE) may be used in the absence of direct head-to-head RCTs or to provide long-term follow up data [170]. A report by CADTH indicated that most HTA agencies have RWE at lower level of evidence hierarchies than RCTs. However, many agencies such as CADTH (Canada), NICE (UK), HAS (France), ZIN (the Netherlands), SMC (Scotland) and AIFA (Italy) consider RWE as suitable supplementary evidence in the support of medicine reimbursement [171]. In Germany, IQWiG considers RCTs in the benefit assessment of drugs, but only uses observational studies in exceptional cases. The use of RWE is under consideration by TGA but currently there is no standard framework available for the submission and assessment of RWE in Australia.

Canada is the only country where high-cost therapies (such as gene or cell therapies), first-in class and medicines for high unmet clinical need undergo a specific review type referred to as 'complex reviews'. This is not a completely separate pathway, as complex reviews are similar to standard reviews in terms of timelines and the steps followed, but evidence from non-randomised trials can be considered after consultation with clinical experts and consideration of any potential ethical and implementation issues [49].

VII. Fast-Track Review/ Early Access

Three countries (France, Italy, and Taiwan) provide earlier access to medicines that treat rare diseases due to the high unmet clinical need. In France, orphan drugs requiring an HTA due to exceeding the likely annual budget impact may be reviewed through a fast-track process, based on the medicine's innovativeness. The innovativeness is determined according to whether the medicine targets a high unmet need and provides a significant clinical benefit. Similarly, the fast-track assessment in Italy can reduce the assessment period of medicines for rare diseases from 180 days to 100 days. AIFA is required to arrange provision and automatic inclusion of medicines for rare diseases into a C-nn (*class* C non-negotiated) (reimbursement is yet to negotiated) which can provide patient access to these medicines before market authorisation is granted or a decision on reimbursement is taken. During this period, the price of the drug can be set by the market authorisation holder and paid entirely by the patient [52]. On the other hand, in Taiwan, orphan drugs can be listed in the NHI Pharmaceutical Benefits and Reimbursement Scheme before market authorisation is granted. However, sponsors are required to apply for market authorisation within three years after being listed, otherwise the medicine will be delisted [20, 22].

Co-dependent Technologies

In many jurisdictions, the reimbursement of codependent technologies (i.e., drugs and tests) are not explicitly linked and they are assessed based on separate submissions. The data suggests that there are only five jurisdictions other than Australia (Belgium, Canada, France, Germany, and UK (NICE)) where integrated and/or parallel process is mentioned for co-dependent technologies.

Australia

The submission of codependent technologies (a companion diagnostic and a targeted medicine) requires advice from two different expert advisory committees (PBAC and MSAC) as listing of the submitted technologies involves funding through two separate reimbursement schemes (the MBS and PBS). There are two different processes for formulating advice: either an integrated or streamlined codependent submission. In the integrated submission, a combined dossier is prepared for the two technologies which is then jointly considered by both PBAC and MSAC. In the streamlined submissions, individual submissions are lodged for each of the technologies at the same time, which are assessed in parallel by MSAC and the PBAC [172].

A very similar process to Australia is followed in Canada for co-dependent technologies, where the technologies (i.e., treatment and diagnostic test (s)) are simultaneously reviewed by CADTH expert committees. There are specific requirements for submission as a co-dependent technology. The sponsors are required to submit a detailed dossier providing evidence for the clinical utility of the diagnostic tests (review of the biomarker status in the study participants) as well as the clinical and cost effectiveness of the drugs. For co-dependent technologies, CADTH may include consultation with additional experts on aspects such as consistency of the testing protocol with current practice, timing of the biomarker testing in the clinical algorithm, and availability and capacity of testing at regional/provincial level [49].

In both Belgium and Germany, joint reimbursement decision making was introduced in 2019 for synchronisation of decision making between the companion diagnostic and reimbursement of the medicines. In Belgium, the application dossier along with the information on the associated medicine is assessed by respective committees (i.e. technical department and CDx Workgroup) within RIZIV, whereas in Germany the Institut des Bewertungsausschusses is responsible for informing the G-BA if any adjustments need to be made in the EBM (Einheitlicher Bewertungsmassstab – catalog for reimbursed services in the public outpatient sector) and facilitates the decision making of the reimbursement of the companion diagnostic [173].

Like in Australia, in France, HAS considers that the validation of the clinical utility of the treatment cannot be dissociated from validation of the clinical utility of the companion test. Therefore, HAS requires that application of targeted molecular therapy must be accompanied by an application for assessment of the companion test. The HAS guidelines specify that for any test to be considered as a companion diagnostic, the predictive utility must be established, or should rely on robust assumptions. The evidence must demonstrate that in addition to targeted treatment being effective in patients with a positive biomarker test, the treatment must demonstrate to be ineffective in patients who do not have the specified biomarker. This implies that the evidence indicating the effect of a treatment in a selected subpopulation with a positive biomarker may only suggest treatment efficacy or lack thereof within this subpopulation. This evidence may not be sufficient to suggest clinical utility of the test

[174]. A study indicated that this perspective allows HAS to only recommend reimbursement of companion diagnostics that have sufficient evidence. From 2015, companion diagnostics that do not have sufficient evidence may be recommended by HAS with CED agreements. It is suggested that it is unlikely that predictive utility can be demonstrated due to the requirement of showing treatment ineffectiveness in patients who are negative for the biomarker [173].

In the UK (besides Scotland), companion diagnostic tests are normally assessed through the diagnostic assessment program. Along with the diagnostic assessment program, the technology appraisal guidelines also provide the criteria for the assessment of companion diagnostics. The sponsors are required to include the costs associated with the diagnostic test in the assessment of clinical and cost-effectiveness of the treatment. This also includes providing sensitivity analysis without the cost of the diagnostic test and an assessment of the diagnostic accuracy of the test for the biomarker of treatment efficacy [27]. In 2022, NICE piloted a new evidence-based approach, early value assessment, to fast-track evaluation of innovative diagnostic tests including companion diagnostics. The purpose is to reduce the timeline of the diagnostic assessment program from 14 months to six months. Furthermore, through this program, selected technologies may no longer need to have a large amount of evidence generated before they can be assessed. Additional reviews may be conducted using a linked evidence approach (as initiated in Australia since 2005) to determine the effectiveness of testing in identifying the eligible patient population for a treatment. The linked evidence approach is adopted when there are no diagnostic effectiveness (clinical utility) data available; the evidence from different parts of the care pathway are linked. NICE indicated adopting a pragmatic approach such as rapid review methods in this program to complete assessments in the given timeline [175].

Antimicrobials

Most countries do not have a special pathway for the reimbursement of antimicrobials, although five countries (France, Germany, Sweden, UK (except Scotland), USA) allow certain exemptions and flexibility in the reimbursement process for antibacterials, which are deemed necessary to combat antimicrobial drug resistance (AMR).

There is no special pathway for the reimbursement of antimicrobials in Australia. The PBAC guidelines do highlight, however, that submissions for new antimicrobials must consider the ‘General principles of antimicrobial use’ contained in Therapeutic guidelines: antibiotic and principles proposed by the Joint Expert Advisory Committee on Antibiotic Resistance for consideration of the target population [176].

In Germany, and France, certain antimicrobials are exempted from HTA as the added therapeutic value is considered established. In France, antibacterials with ASMR Level IV (minor) are granted exception from the ASMR based evaluation framework. Usually, those medicines with a higher or moderate added therapeutic benefit cannot have a price lower than the lowest prices across the comparative countries. This was extended to antibacterials with minor added therapeutic value (ASMR level IV) as they are

deemed important for combating AMR. Moreover, in France, pharmaceutical companies are also required to make payments to the social security budget if their year-on-year turnover increase exceeds a specific level. Sales of antibiotics required to combat AMR are excluded from companies' liable turnover, to provide them incentive to produce antibiotics [177].

In Germany, from March 2020, reserved antibiotics were exempted from the normal benefit assessment process, as they automatically qualify as providing added therapeutic value, allowing exemption from price control and a faster access to market. This also means that they are exempted from being included in internal reference pricing groups. A legislation was also introduced in 2017 that allows IQWiG and G-BA to consider the resistance patterns when determining added therapeutic value. This has allowed price negotiation for some new antimicrobials that have claimed non-inferiority and may not have evidence for added therapeutic value, rather than including them in the reference pricing group [177].

In 2018, the Swedish government commissioned the Public Health Agency of Sweden (PHAS) to pilot a supply-based reimbursement process of antibiotics with significant medical value and ensure patient access to antibiotics required to treat drug-resistant infections. The antibiotics selected for this pilot program should have special medical value, risk of lack of availability on the Swedish market and annual sales must not have exceeded SEK 4 million during the previous year 2019. In this supply-based reimbursement model, the national government guarantees a minimum annual revenue to the manufacturers of selected antibiotics and in return, the company is required to ensure the supply and stockpile of selected antibiotic within an agreed time frame. In this model, the reimbursement of antibiotics was partially de-linked from the sales revenue. The results of this pilot program were presented to the Swedish government in March 2023 and official implementation of this model is under consideration [178].

Like Sweden, in collaboration with NHS England, NICE has recently established a new HTA process and a subscription style payment model for 2 antimicrobial products namely cefiderocol and ceftazidime–avibactam. Under this model, payments made to the sponsors is based on value of the drugs to the NHS which is measured in quality-adjusted life-years (QALYs) rather than the volume of the drug sold. Unlike usual economic analyses that consider value of the medicine over the lifetime of treated patients, this delinked subscription model estimated the incremental net health effects (INHE) of antimicrobials to the NHS over the product lifetime. This informed negotiations between sponsors and NHS (England) based on the annual value over a 10-year contract period. This process is currently under public consultation and the feedback received will determine whether this process will be adopted in the future [179]. Furthermore, along with the changes in payment model, a new broader value HTA process was also trialled for antimicrobials based on a framework known as STEDI (Spectrum, Transmission, Enablement, Diversity, and Insurance value) [180]. The different elements of this framework are defined as:

i. *Spectrum*: Benefit associated with use of narrow spectrum antibiotics and resulting prevention of antimicrobial resistance.
ii. *Transmission*: Indirect benefit of reduced infection rates by reducing onward transmission of infection.
iii. *Enablement*: Benefit associated with improving outcomes of other treatments where antibiotics may be needed.
iv. *Diversity*: Indirect benefits of preserving the diversity and activity of existing antibiotics for longer.
v. *Insurance*: Indirect benefits associated with having an antibiotic treatment as a last line option for patients in whom all other treatments fail and dealing for major outbreaks.

In addition to the outcomes relevant to standard medicine assessment, these elements are also considered in the HTA of antimicrobials.

This may include benefits to those who do not become infected or those who are treated with antimicrobials and able to have other treatments like chemotherapy, and surgery, or those who may not have existing treatment options due to antimicrobial resistance. Data are expected to be derived from modelling studies and/or epidemiological studies rather than clinical trials [180].

In USA, specific reimbursement information for antimicrobials is not available, however, the FDA can grant a 'qualified infectious disease product' (QIDP) designation for certain antibiotics under Generating Antibiotic Incentives Now (GAIN) Act of 2012. Through this designation some antimicrobials can have five additional years of market exclusivity as well as expedited approval through fast-track review. This expedited approval with market exclusivity is only for antimicrobials that target a certain list of 'qualifying pathogens' or treat drug-resistant pathogens [177].

Submissions with no sponsor

Only Canada reported a separate review process for non-sponsored applications. This review process is initiated after public drug programs from provincial and territorial governments request a review and recommendations for a specific medicine from CADTH's Formulary Management Expert Committee (FMEC) in situations where an eligible sponsor does not apply for reimbursement. For any medicine to be considered for non-sponsored review, the sponsor must have declined to submit an application (or resubmission), the medicine must be in the later stages of the technology lifecycle - based on information from a drug registry and/or patent registry - and enough clinical evidence needs to be available to allow CADTH to evaluate the effectiveness of the medicine, and it must have received a positive funding recommendation internationally. The review process comprises of specifying a protocol (i.e., PICO) and then conducting one or more independent systematic reviews according to the protocol and a cost comparison between the medicine and the appropriate comparator(s). The stakeholders (including sponsors) are engaged in the same way as sponsored reimbursement reviews. After considering the feedback received, the medicine can receive a positive, negative,

or conditional reimbursement recommendation [181]. The sponsor would, of course, need to agree to supply the medicine.

HTA pathways for vaccines

There is an increasing recognition in the academic literature and the main jurisdictions included in our analyses that the value assessment of vaccine needs to consider factors that go beyond the scope of HTA. This is in line with the guidelines published by the WHO that highlights the need to capture value delivered to the individual, society, and the broader economy [182]. The evaluation of vaccines frequently involves a different process than the HTA of medicines. Therefore, the assessment process for vaccination in key jurisdictions (Australia, Canada, France, Germany, South Korea, Taiwan, The Netherlands, UK, and USA) is outlined in Table 8.

With respect to the process of evaluating vaccines, we focused on the following questions:

- Who initiates the process e.g., National Immunisation Technical Advisory Group (NITAG), Sponsor, Ministry of Health, or other stakeholders?
- Who conducts the assessment of the evidence and how?
- Who takes the final decision regarding funding and inclusion of the vaccine into the NIP?
- What is the timeline for assessment and listing of the vaccine on the NIP?

Table 8 Pathways for vaccines in key jurisdictions

Jurisdiction	Health care financing and delivery	HTA system			Timing of key milestones in the HTA pathways*		
	Who is/are the payer/s for vaccines?	***Who initiates the process?***	***Who conducts the assessments?***	***Who conducts the appraisal OR makes the decision***	***Time taken to reach funding decision (weeks / number of rounds)?***	***Time taken for patients to have funded access (weeks)?***	***Frequency of committee meeting***
Australia	Majority of cases: Provided through National Immunisation Program (NIP)	Sponsors Horizon scanning by Australian Technical Advisory Group on Immunisation (ATAGI)	External evaluation groups (universities/academia)	Australian National Immunisation Technical Advisory Groups (final assessment) (ATAGI) (appraisal) PBAC (appraisal) Minister of Health (decision)	22 weeks (ATAGI) + normal PBAC cycle (17 weeks)	○	ATAGI: Six times a year Ad-hoc meetings: Not available
Canada	Federal & provincial and territorial (P/T) governments (Immunisation Partnership Fund (IPF))	National Advisory Committee on Immunisation (NACI) Other stakeholders	National Advisory Committee on Immunisation (NACI)	Public Health Agency of Canada (PHAC)	No defined timelines	No defined timelines	NACI: Three times a year Ad-hoc meetings: Available
France	Provided through Vaccination schedule	Sponsors HAS, when referred by patients' associations, professional college, and associations. Horizon scanning	HAS: Vaccine Committee (CTV)	HAS: CT and CEEPS (appraisal) Minister of Health (decision)	○	○	○

Jurisdiction	Health care financing and delivery	HTA system			Timing of key milestones in the HTA pathways*		
	Who is/are the payer/s for vaccines?	***Who initiates the process?***	***Who conducts the assessments?***	***Who conducts the appraisal OR makes the decision***	***Time taken to reach funding decision (weeks / number of rounds)?***	***Time taken for patients to have funded access (weeks)?***	***Frequency of committee meeting***
Germany	Sickness funds (National Immunisation Program)	Standing Committee on Vaccination (*Ständige Impfkommission* - STIKO)	Standing Committee on Vaccination (*Ständige Impfkommission* - STIKO) & Immunisation Unit at Robert Koch Institute (RKI)	G-BA	No defined timelines	No defined timelines	STIKO: Two times a year Ad-hoc meetings: Available
South Korea	Routine service: National Immunisation program (NIP) Ad-hoc: Supplementary vaccines (dealing with emergence)	Korea Expert Committee on Immunisation Practices (KECIP) Korea Disease Control and Prevention Agency (KCDC) Horizon scanning	12 Sub-committees of KECIP and/or special working groups	Appraisal: KECIP (Appraisal) Minster of Health (decision)	○	○	KECIP: Two times a year Ad-hoc meetings: Available
Taiwan, Republic of China	National Immunisation Program (NIP), funded by National Vaccine Fund (NVF)	The Advisory Committee on Immunisation Practices (ACIP) Taiwan Centers for Disease Control (CDC) Department of Health	Working groups in ACIP	ACIP (Appraisal) Minster of Health (decision)	○	○	ACIP: Two times a year Ad-hoc meetings: Available
The Netherlands	National Immunisation Program (NIP) & Dutch Drugs Reimbursement System	Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport VWS)	Committee on Vaccine within Health Council of Netherlands (*Gezondheidsraad* [GR]) (NITAG) National Health Care Institute (Zorginstituut	Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport VWS)	No fixed timeline	No fixed timeline	○

Jurisdiction		Health care financing and delivery	HTA system			Timing of key milestones in the HTA pathways*		
		Who is/are the payer/s for vaccines?	***Who initiates the process?***	***Who conducts the assessments?***	***Who conducts the appraisal OR makes the decision***	***Time taken to reach funding decision (weeks / number of rounds)?***	***Time taken for patients to have funded access (weeks)?***	***Frequency of committee meeting***
				Nederland [ZIN]) (HTA Agency)				
United Kingdom	England	NHS (National Immunisation Program)	NITAG (JCVI); PHE (Public Health England) Department of Health and Social Care Market authorisation holder	Joint Committee on Vaccination and Immunisation (JCVI)	*Department of Health and Social Care*	No defined timeline	No defined timelines	<u>JCVI:</u> Three times a year <u>Ad-hoc meetings:</u> Not available
	Wales	Follows JCVI advice						
	Scotland & Northern Ireland	Health Departments can choose to accept the JCVI's advice						
USA		Medicare (Plan B & D) for individuals aged 65 and above and younger adults with long-term disabilities. Medicaid for low income American Private Health Insurance Vaccines for Children Program Department of Veteran Affairs	Centre for Disease Control and Prevention (CDC)	Advisory Committee on Immunisation Practices (ACIP)	Centres for Disease Control and Prevention (CDC), US Department of Health and Human Services.	No fixed timeline ACIP meeting held three times in a year	No fixed timeline	<u>ACIP:</u> Three times a year <u>Ad-hoc meetings:</u> Available

ATAGI = Australian Technical Advisory Group on Immunisation; NACI = National Advisory Committee on Immunisation; Public Health Agency of Canada (PHAC); CTV = Vaccine Committee; STIKO = Ständige Impfkommission; RKI = Immunisation Unit at Robert Koch Institute; KECIP = Korea Expert Committee on Immunisation Practices; KCDC = Korea Disease Control and Prevention Agency; ACIP = The Advisory Committee on Immunisation Practices; GR = Committee on Vaccine within Health Council of Netherlands; NITAG = National Immunisisation Technical Advisory Group; PHE = Public Health England; JCVI = Joint Committee on Vaccination and Immunisation

CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Australia

In Australia, vaccines are fully reimbursed if they are listed in the National Immunisation program (NIP) [183]. HTA is needed for the reimbursement of vaccine when: 1) it is a new vaccine, or, 2) the existing NIP listed vaccine is proposed for an extension of cohorts. The Australian Technical Advisory Group (ATAGI) is a non-statutory committee with a key role in providing the PBAC with technical advice for listing a vaccine on the NIP [184]. The external vaccine evaluation groups comprising of experts in immunisation, clinical medicines, and epidemiology are commissioned to conduct assessment and provide recommendations for vaccine inclusion in the NIP. These recommendations are discussed and appraised at an ATAGI meeting to finalise its advice to PBAC regarding the inclusion of a vaccine in the NIP [184]. Taking into consideration the ATAGI advice, PBAC provide its recommendations to the MoH regarding the funding of the vaccines[185]. Prior to the vaccine submission to PBAC, the ATAGI advice must be included in the submissions, and the issues raised at the ATAGI meeting need to be addressed [185]. The HTA process for vaccine reimbursement can be initiated by sponsor by submitting an application to PBAC or TGA (parallel processing) [186], or by ATAGI through horizon scanning [185].

Along with the NIP, a vaccine can also be reimbursed through PBS listing. However, it is not common and PBS listing may not offer full coverage. Specifically, these are vaccines that have been proven 'discretionary' for the majority of the population (e.g., travel vaccine), or where the eligibility of vaccination is difficult to determine[187]. The National Centre for Immunisation Research and Surveillance (NCIR) develops the clinical guideline for vaccines [188].

ATAGI meetings are held six times in a year [185]. From the sponsor's submission to ATAGI advice takes 20 weeks with an additional two weeks to deliver ratified advice to sponsors and the PBAC. Sponsors are required to lodge a submission to PBAC within 9 weeks of receipt of ATAGI advice [184]. PBAC can also request additional ATAGI advice on matters highlighted during the evaluation. The guidelines are available for sponsors to prepare the submission [189]. The vaccine submission must consider the following factors:

- Indicate target population for the proposed vaccine (i.e., within a specific age cohort)
- Target population must be selected based epidemiology of the vaccine-preventable disease (VPD) (i.e., consideration of risk factors such as age, gender, ethnicity)
- Reason/s to maximise population coverage as the proposed vaccines is anticipated to result in indirect protection (herd immunity) of unimmunised individuals by reducing one or more of the following:
  1) Carriage of the pathogen
  2) Proportion of susceptible individuals
  3) Transmission of the pathogens.

However, similar to the reimbursement decisions for medicines, the criteria and threshold related to specific reimbursement decisions for vaccines are unknown [187]. The outcomes of PBAC meetings are published online and can be accessed by the public, in the form of a *Public Summary Document*, including the rationale for PBAC decisions.

Canada

An expert advisory group, the National Advisory Committee on Immunisation (NACI) provides scientific, medical, and public health related advice to the Public Health Agency of Canada (PHAC) relating to vaccines. Historically, NACI used to base its advice regarding vaccine effectiveness and safety on scientific factors such as disease burden and vaccine characteristics [190]. However, in 2019, PHAC expanded the scope of NACI evaluation to include programmatic factors such as cost, ethics, feasibility, and acceptability in the decision making. For this purpose, an EEFA (Ethics, Equity, Feasibility, Acceptability) framework was developed based on the analytical framework posed by Rickson and colleagues for systematic consideration of programmatic factors in decision-making. This framework provides a minimum threshold for consideration of different programmatic factors and how and which aspects to consider and when further in-depth analysis is required. Furthermore, it also provides matrices to identify distinct and potential issues with respect to ethics, equity, feasibility, and acceptability that may arise and interventions to resolve these issues [96].

Before conducting an economic analysis, prioritisation of topic questions is carried and to determine which questions need analysis and which can be deferred. The purpose is to support timeliness and the quality of vaccine recommendations. The members of NACI and the Canadian Immunisation Committee (CIC) rank the economic need for each question as high, moderate, or low based on stakeholders (including public, clinicians and industry) needs. The research questions ranked as high or moderate need are further assessed, based on burden of disease and proposed benefit of the vaccine program. This is done through consensus by the NACI secretariat, Working group Chair/Vice chair and other relevant subject matter experts. On completion, research questions are ranked as recommended for economic analysis, deferred, or not recommended to be prioritised. The economic evaluation is based on the CADTH guidelines; however, it has been amended where necessary. The main difference between the economic evaluation of vaccines by NACI and other health technologies by CADTH is consideration of population-level factors. This stems from an assessment of impact on both vaccinated and unvaccinated individuals. For instance, the NACI guidelines recommend economic evaluation from two reference cases perspectives: a publicly funded health system perspective and a societal perspective. The societal perspective mainly focuses on factors related to those not directly vaccinated and non-health sectors. This can include aspects such as societal cost-effectiveness and translating broader societal impacts into economics analyses [191].

NACI meet face-to-face three times in a year, however, ad hoc teleconference can be arranged as needed. The topics for evaluation can be submitted by committee members and other stakeholders. The recommendations are developed by working groups within NACI through synthesis of the body of evidence of benefits and risks of the vaccine, relevance and quality of the evidence, the strength of association, economic and EEFA factors. Different external expert groups can be commissioned to conduct literature review and knowledge synthesis. Following the synthesis of the evidence, the working groups prepare a draft statement and recommendations for consideration and voting by NACI. The final statement, incorporating the committee discussion and vote is then sent to Chief Public Health Officer and published after approval on PHAC website and in the *Canada Communicable Disease Report*.

France

In France, vaccines are reimbursed through the National Immunisation Program (NIP) [192]. Along with the medicines, HAS also conducts assessments for vaccine reimbursement. The Technical Commission on Vaccinations (Comité Technique des Vaccinations [CTV]) is one of the standing committees within HAS responsible for providing recommendations on the inclusion of vaccines into the NIP [193].

The HTA process for reimbursement is initiated by sponsors by applying to both HAS and Ministry of Health (MoH). The submission must specify if the proposed intervention is a new vaccine program or an update/extension to an existing one. Moreover, the MoH, approved patient associations, professional college, and societies can also request HAS for a recommendation regarding inclusion of the vaccine in the NIP [194]. Additionally, CTV conducts horizon scanning annually to identify upcoming vaccines [195]

The CTV provides recommendations on the funding and inclusion of vaccines into the NIP based on clinical, economic, and population-based aspects. The clinical aspects are based on efficacy, safety, and tolerability, whereas the economic analysis takes into consideration the cost-effectiveness. Along with the CTV, the TC also conduct a clinical assessment based on a vaccine-specific evaluation framework. This framework takes into consideration factors such as burden of disease, clinical effectiveness, tolerability, and safety [195]. The TC determines the public health benefit for the vaccine on a case-by-case basis rather than through the specific matrix used for other medicines when defining high unmet need [69].

The TC clinical assessments are supported by economic evaluations conducted by CEESP but only in cases where a vaccine is considered innovative (at least ASMR level I – III claimed by the sponsor) and have a significant impact on the organisation of care and the statutory national health insurance budget [194]. The budgetary impacts are defined as expected expenditure of EUR20 million or greater. The final decision on the reimbursement and inclusion into the NIP is taken by the MoH.

HAS also offers early scientific advice for vaccines developed for a disease with an unmet clinical need, vaccines proposing new mode actions and for submissions with

results of a Phase II trial available. Generally, sponsors want HAS advice before starting a Phase III trial. The CTV can be involved in this process but do not provide any formal advice. The process involves face-to-face meetings and document exchange between sponsors and HAS, with HAS providing its final advice within four months [195].

Germany

The Robert Koch Institution (RKI) in Germany annually conducts horizon scanning for vaccines and discusses with the market authorisation holder whether there is new evidence on the effectiveness of the vaccines. The process of assessment is initiated by the German NITAG, the Standing Committee on Vaccination (*Ständige Impfkommission* [STIKO]) within RKI. The main factor in the development of a STIKO recommendation is a risk-benefit analysis of the vaccine. Along with risks and benefits for an individual receiving the vaccine, STIKO consider risks and benefits at the population level. This may include herd immunity protection effects, age distribution of cases or potential pathogen replacement phenomena. The evidence-based medicine framework comprising of a systematic review of the literature is utilised to assess vaccines and develop recommendations. The evidence is identified through systematic searches of peer and grey literature. STIKO also uses the approach of the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) Working Group. The usual comparator in such analysis is "no vaccination"; however, alternative preventive measures may also be considered in developing vaccine recommendations [196].

The topic for assessment can be recommended by the executive secretariat of STIKO (through horizon scanning), the Ministry of Health and medical societies. However, due to limited resources and personnel, topics are prioritised based on the availability of the vaccine on the German market, public interest, disease burden, benefits/risks of a new vaccination program and availability of evidence on vaccine effectiveness and safety. STIKO establish topic-specific working groups (WG) which consist of a panel of external experts, STIKO members and representatives of the STIKO executive secretariat. The working groups define a set of questions in the form of PICO to define the scope of the assessment. The questions are mostly related to relevance of the assessment (public interest), pathogen (characteristics, subtypes/serotypes), indication (prevalence, incidence, hospitalisation, mortality), vaccine (scope of licensure, effectiveness, safety) and immunisation strategy and implementation [196].

Once STIKO working groups have prepared their advice, it is sent to stakeholders such as G-BA and local health authorities for appraisal. In finalising its recommendations on funding, STIKO considers these comments in a closed meeting conducted at least two times in a year [197]. The summary of STIKO recommendations is published annually in the national epidemiological bulletin of the RKI. The G-BA makes the final decision on funding the vaccine through sickness funds, based on STIKO recommendations. However, the G-BA can disagree with the provided recommendations due to reasons

unrelated to clinical or cost effectiveness. Unlike medicines, G-BA does not conduct a formal HTA of vaccines [196, 198].

South Korea

Vaccines in South Korea are funded under two streams: National Immunisation program (NIP) stream, and supplementary vaccines stream. The NIP includes vaccinations for children under age 12, and the supplementary vaccines provide coverage for ad-hoc service in response to outbreaks or emergence of an infectious disease [199]. The Korean Centre for Disease Control and Prevention (KCDC) is responsible for implementation of new vaccine policy and budget management of immunisation programs. The Korean Expert Committee on Immunisation Practices (KECIP) is the national immunisation technical advisory body in Korea, comprising of experts from different areas such as in clinical medicines, epidemiology, and immunisation programs [200]. There are 12 sub-committees of KECIP, who undertake the assessment, including collating and analysing evidence, and providing policy recommendations. For some topics, specific working groups can be established [200]. Once the sub-committee reviews the epidemiological, vaccine, and economic data, members try to reach consensus for recommendations. However, if all members cannot reach a consensus, the Chairperson makes the final decision on what recommendations to provide to the KECIP. The KECIP members appraise and discuss assessment reports prepared by subcommittees/working groups and relevant issues to finalise committee recommendations. The final decision regarding funding is made by the Ministry of Health and Welfare (MoHW) [200]. KECIP recommendations are not legally binding, but in most cases the MoHW approves KECIP recommendations. If there is a need to revise laws or there is a lack of available funds for vaccine coverage, occasionally the MoHW may not implement KECIP recommendations.

After the recommendation is approved by MoHW, KCDC is responsible for implementing the policy, including designing program plans, developing the associated budget, and liaising with local or private health facilities [200].

The meeting agenda for KECIP is set by the Director of the Division of Vaccine-Preventable Disease (VPD) control and the NIP in the KCDC, where the topics comes from a range of professionals including KECIP members, KCDC staff, members of KECIP sub-committees, and other experts [200]. The KECIP meetings are held twice in a year but ad-hoc meetings can be arranged if required [200]. The meeting agenda is published, and the meeting can be open to the public at the discretion of the KECIP chairperson [200]. National guidelines and immunisation schedules are published by KECIP regularly.

Taiwan

In Taiwan, vaccines included in the National Immunisation Program (NIP) are funded by the National Vaccine Fund [201]. The Advisory Committee on Immunisation Practices

(ACIP) make recommendations on vaccine reimbursement based on the disease severity, disease burden, clinical and cost-effectiveness and safety of the vaccine [202]. ACIP comprises of experts nominated by the Taiwan Centres of Disease Control (CDC). The topic for assessment can be proposed by members of ACIP, CDC, or the Department of Health [202]. The assessments are carried out by different working groups within ACIP, specialising in a specific topic [202]. Working groups are responsible for collecting evidence and synthesising findings relevant to the topic. In some cases, opinions from experts can be sought [202]. The assessments are considered within the ACIP meeting to make recommendations [202]. After the ACIP has issued its advice on the inclusion of a vaccine into the NIP, the Taiwan CDC is responsible for the implementation of the vaccine program [202]. According to the law, the procurement of new vaccines must be initiated within one year of an ACIP recommendation [202].

The ACIP meets at least two times a year, and additional meetings can be held if required [202]. Minutes of each ACIP meeting are published online along with the summary of the recommendations, vaccine schedule and description of the target population [203].

The Netherlands

In the Netherlands, the vaccines are usually reimbursed through the National Immunisation Program (NIP). However, a study indicated that the Drugs Reimbursement System ("Geneesmiddel Vergoedings Systeem", GVS) has also received applications for the inclusion of vaccines, that are not yet part of NIP, into the drugs reimbursement list [204]. Under the NIP, residents with valid health insurance will receive most vaccinations free of charge. The NIP ensures that vaccines are fully covered for children and high-risk groups (i.e., individuals aged 60 years or above and/or with underlying conditions such as cardiovascular diseases, kidney diseases, diabetes, lung disease or a compromised immune system). Despite high vaccine coverage, there is some regional variation.

The process of vaccine assessment is initiated by the Dutch Ministry of Health, Welfare and Sport (VWS) based on topics identified through horizon scanning, which is conducted twice a year. The Committee on Vaccinations (CoV), within the Health Council of the Netherlands (*Gezondheidsraad* [GR]), is an independent scientific committee that is legally mandated to provide advice to the VWS on the inclusion of vaccines on the NIP [205]. The work of CoV is supported by the National Institute for Public Health and the Environment (*Rijksinstituut Volksgezondheid en Milieu*) which collates evidence on vaccine effectiveness and safety. In this process, ZIN is also involved as an HTA body and carries out assessments of vaccines in parallel with CoV [195]. The assessment by CoV is based on a framework outlined in an advisory report published in 2013. According to this framework, the inclusion of a vaccine in public programmes must be based on the following criteria [205, 206]:

i. *Severity of the disease*: the extent of disease burden for individuals and at a population-level

ii. *Vaccine effectiveness and safety*: vaccine effectiveness in the prevention or the reduction of symptoms and adverse events associated with vaccination (if any)
iii. *Acceptability:* the inconvenience that an individual may experience with the personal vaccine or the vaccination programme as whole, is not disproportionate to the health benefits obtained from the vaccine by the population and the individuals concerned.
iv. *Efficiency*: the cost-benefit ratio of vaccination compares favourably to the cost-benefit ratio of other interventions targeted at reducing the relevant disease burden.
v. *Public health need*: vaccine is targeting a potentially public health need.

These criteria are applied in a stepwise fashion with each step assuming that the preceding step/criterion was answered in the positive. For instance, there is no need to address the cost-effectiveness of a vaccine until it is identified to be clinically effective and safe for the target population. There are no defined timelines for the development and implementation of GR recommendations [206].

In parallel with the GR evaluation, ZIN also conducts assessments of vaccines based on clinical, economic, and population-based aspects. The clinical assessment includes factors such as the burden of disease, clinical effectiveness, tolerability, and safety whereas economic assessments take into consideration cost-effectiveness and budget impact. ZIN may also provide formal scientific advice in parallel with a regulatory body. The process involves face-to-face meetings between sponsors and ZIN members and the exchange of documents based on the submission guidelines. This process may take six months from the date of the letter of intent to the issuance of final advice by ZIN [195].

Both GR and ZIN recommendations are considered by VWS for inclusion of a vaccine into the NIP and for a national tender for procurement. For some vaccines, reimbursement levels may be established for a specific subpopulation.

United Kingdom

England and Wales

The Joint Committee on Vaccination and Immunisation (JCVI, the Committee) is an independent departmental expert committee and a statutory advisory body that advises the Secretary of the State on the provision of vaccines. The topics for assessment by the JCVI, such as the evaluation of a new immunisation program or modification to an existing program, are identified through horizon scanning performed annually by the committee. The Department of Health and Social Care and Public Health England (PHE) can also suggest topics to JCVI for assessment following consultation with health professionals or the public. The JCVI subcommittee uses NICE methods to assess the clinical and cost-effectiveness of vaccines. Using the NICE approach, a vaccine program can be considered cost-effective if the health benefits are more than the opportunity costs (measured as health benefits of displacing healthcare services to fund the

vaccination program under consideration) [207]. The health benefits assessed include both direct health benefits to the vaccinated population and the indirect health benefits to an unvaccinated population (e.g. herd immunity).

The process involves comprehensive searches and appraisal of available evidence from varying sources such as published and unpublished literature, advice from other national and international bodies, commissioned clinical, operational, epidemiological, and economic analyses, and evidence provided by stakeholders. The evidence may also e submitted by sponsors or academic groups to JCVI as commercial or academic-in-confidence information. In cases where JCVI need an external clinical, epidemiological and/or economic analysis, JCVI may commission the National Vaccine Evaluation Consortium and Centre for Infections within PHE, independent academic groups or the NIHR Public Health Research Program (for clinical analyses only).

The evidence presented to JCVI and reports on commissioned studies are discussed at the committee meetings and the validity and relevance of the evidence are established, based on factors such as the quality of the evidence, selection of participants, measurement of the outcomes, risk of bias, statistical analyses, plausibility, and uncertainty in the outcomes. The JCVI committee meetings are conducted three times a year [208]. Once JCVI has established its opinion based on the evidence, an interim statement may be issued for a short period (usually one month) for consultation with the stakeholders who provided the evidence. JCVI considers the responses of these stakeholders in preparation of its advice. The committee's advice is then communicated to the UK health departments and PHE and published.

In instances where there is uncertainty about the evaluation and procurement of a vaccine, a Working Group on Uncertainty in Vaccine Evaluation and Procurement is established to advise health departments and JCVI. The working group considers how the cost-effectiveness was evaluated, the implications of the uncertainty (if any) for the procurement process, and provide appropriate relevant advice to the health departments [207].

Scotland and Northern Ireland

JCVI advises the NHS in all four UK countries (England, Wales, Scotland, Northern Ireland) regarding different aspects of the immunisation program. Although JCVI has no legal basis for providing advice to Ministers in Scotland or Northern Ireland, health departments from these countries may choose to accept the Committee's advice or recommendations. For instance, in Scotland, the Scottish Government Health Directorates sets the immunisation policy based on JCVI policy.

United States of America

In the United States, vaccines are funded through multiple public and private insurance plans. Under Plans B and D, Medicare provides coverage for vaccines for individuals aged above 65 years and young adults with long-term disabilities. The patient's out-of-pocket payment, vaccine pricing and providers' reimbursement may vary across both Medicare plans. Around 55% of American residents are covered for vaccines through private insurance, such as employer-sponsored insurance. All such insurance plans are subject to certain standards and coverage requirements specified in the Affordable Care Act (ACA). There is also a special federal program, Vaccine for Children (VFC), that provides coverage for the vaccination of eligible children. The Centers for Disease Control and Prevention (CDC) purchases vaccines directly from manufacturers and distributes them to local health departments. These health departments are then responsible for providing these vaccines to VFC partner public health agencies and physicians' offices at no charge. Additionally, Medicaid provides coverage for vaccines for low-income individuals. However, coverage varies across States based on age and eligibility criteria. The federal government also purchases a limited number of vaccines for uninsured individuals under Section 317 of the Public Health Services Act [209].

The Advisory Committee on Immunisation Practices (ACIP) is a federal advisory committee within the Center for Disease Control and Prevention (CDC) that develops recommendations on the use and provision of vaccines. ACIP comprises 15 members with expertise in vaccinology, immunology, paediatrics, internal medicine, nursing, family medicine, virology, public health, infectious diseases, or preventive medicine. In the preparation of recommendations, the committee takes into consideration factors such as disease burden and epidemiology, vaccine effectiveness, safety, strength and quality of evidence, economic analyses, and implementation aspects [210]. ACIP uses an Evidence to Recommendations (EtR) framework based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to develop recommendations. The framework consists of the following domains [211]:

- Public Health Priority: Prevalence and incidence of disease, mortality and morbidity and social impact
- Benefits and harms of vaccine: magnitude of effect, adverse effects, balance between benefits and harms and certainty of evidence
- Perception of value: perspectives and perceptions of target population about the vaccine, and uncertainty around value.
- Acceptability
- Cost-effectiveness
- Equity
- Feasibility

The working groups within the ACIP are responsible for collecting, assessing and collating evidence, based on the EtR framework. The information collated by working groups is then discussed in ACIP meetings which are held three times a year. These meetings are open to the public. During these meetings, members review the evidence

and clinical trial results presented by the working groups and discuss the effectiveness and safety of the vaccine. The economic evidence must be submitted to ACIP working groups eight weeks prior to the ACIP meeting date for a technical review by ACIP and CDC Work Group leaders and economists. Only if the economic analyses are approved by economists, can these be presented to the ACIP working group for consideration before presentation to ACIP meetings [212]. After consideration, ACIP provides a set of recommendations to the CDC on vaccine provision. Once these recommendations are approved by CDC Director, they are published in the CDC's Morbidity and Mortality Weekly Report (MMWR) [210].

Summary of Key Points

Australia is one of the few countries where the recommendations for the inclusion of vaccines into the NIP do not directly come from a NITAG (ATAGI) but also requires review by the PBAC (HTA body). This results in an average time from market approval to listing on the NIP of 48 weeks as compared to 17 weeks for medicines. A similar process is seen in the Netherlands where both the advisory committee and HTA agency are required to conduct assessments separately. However, both processes are conducted in parallel, and recommendations from each agency/committee are considered by VWS for final decision-making.

To reduce timelines and manage resources, Canada and France conduct economic analyses for specific vaccines where there is a need. In France, the CEESP committee only conducts economic analysis for vaccines that are claimed to be innovative by sponsors (at least ASMR level I – III) and have a significant budgetary impact (expected cost of EUR20 million or greater in a year). The NACI committee in Canada prioritises policy questions to determine which vaccines are prioritised for economic evidence and which can be deferred, in order to support the timeliness and quality of vaccine recommendations. The need for economic analyses for each research question is established based on the burden of disease and the proposed benefit. Similarly in Germany, topics for vaccine assessment are prioritised to determine the order in which each topic will be addressed by topic-specific working groups. The criteria for topic prioritisation are based on three factors: availability of the vaccine in Germany, disease burden, and availability of evidence on clinical and cost-effectiveness.

In most countries, the assessment of vaccines is limited to health benefits for the vaccinated population, the number of cases avoided, and the cost associated with the vaccination program. It has, however, been argued that the value of vaccines extends beyond the vaccinated population and, consequently, that vaccination programs can be undervalued in HTA assessment [213]. Therefore, there is a need to explicitly consider the broader value of vaccination for the healthcare system and society. Specifically in Canada, NACI guidelines recommend that an economic evaluation is conducted from two reference case perspectives: publicly funded health system perspective and societal perspective. This helps in consideration of the health benefits for the unvaccinated, and

the cost off-sets to the health system and non-health sectors (e.g., productivity-related impact).

In addition to patient-related factors, NITAGs in Canada, Germany, the Netherlands, the UK, and the USA also consider the acceptability of the vaccine and implementation aspects in the assessment of a vaccination program. An EEFA framework has recently been employed in Canada to consider access and equity issues in vaccination programs. Through this framework, NACI not only assesses the acceptability and feasibility of vaccine programs but also carries out equity and ethics analyses. The factors considered by NACI associated with possible health inequalities are socioeconomic status, race, geographic location, occupation, gender identity, religion, education, pre-existing conditions, age, and other risk behaviours such as the use of drugs and alcohol and smoking. It also takes into consideration how social determinants may impact susceptibility, exposure, and disease severity of infectious diseases [96, 190].

STAKEHOLDER WORKSHOPS: THEMES THAT HAVE BEARING ON CURRENT HTA PATHWAYS AND PROCESSES

Several key themes emerged from the workshops conducted with public servants, committee members, evaluation groups and industry sponsors involved in the current HTA process. These themes are summarised briefly below.

What in the current Australian HTA process is working well?

- The system is predictable – everyone knows what is going to happen, when and who is involved. The timing is predictable being built around three 17-week cycles. There are guidelines and templates available for promoting consistency in the presentation of evidence and consistency in decision making.
- The Public Summary Documents are a useful resource and provide a significant amount of information.
- Version 5 of the PBAC Guidelines provides helpful guidance.
- The process for evaluating codependent technologies, including the alignment between PBAC and MSAC, works well, although there can be delays.
- The parallel process is an excellent initiative that has reduced the time to access when compared to submissions undergoing a sequential process.
- Incorporation of the patient perspective into the HTA process is positive.
- There are (rare) examples of medicines that have had rapid PBS listing following registration when there has been clear unmet clinical need and the trial results are positive. The system can move fast when there is a need. The key is early engagement and all stakeholders working together towards a common goal.

- With regards to reducing the time from positive PBAC recommendation to PBS listing, the Pathway A works well i.e., where the submission is case managed by the Department.

What in the current HTA process needs changing?

Stakeholders indicated that there are a range of issues with current processes that could be addressed. These include:

- *Rare diseases and Real-World Evidence (RWE)* - The current approaches to assessing and funding medicines in small populations is not ideal as small populations/rare diseases are disadvantaged in the evidence base that is available and may not be cost-effective. Observational data, single-arm studies and the like are more likely to be used for rare diseases and other therapies where head-to-head trials are unlikely to be run. The quality of these data is often poor. PBAC does show pragmatism sometimes in decision making, but there are improvements that can be made to the way in which RWE could be considered during the evaluation process. There is opportunity for international harmonisation and collaboration with RWE guidance for HTA already implemented or in development in the UK (NICE) and Canada (CADTH).
- *Uncertainty* - This can be dealt with using managed access programs (MAP) and coverage with evidence development (CED). However, these have had mixed success to date.
    - *MAPs*: The price is typically low in a MAP – as the price is used as a lever to deal with uncertainty – and a low price may not be approved by the global headquarters of the medicine sponsor. However, it was also noted that MAPs may in fact be replacing the compassionate access programs that industry already offers. There is inherent risk to the sponsor with a MAP because the real-world results may not reflect the trial results or will be less convincing in the target population. Also, data collection can be onerous and there is no infrastructure for the easy collection and submission of data. Pay-for-performance data are, however, essential in addressing clinical uncertainties and so the data collection aspects need to be resolved.
    - *CED*: There is a risk that while the evidence is being collected, from a global perspective, the context changes – new technologies are being developed and new studies produced. Medicine sponsors may not want to invest in CED programs in multiple countries. If CED data are produced it might not be produced in, or for, Australia. The question was posed whether the PBAC would accept CED data from the UK or Canada, or other comparable countries. It was suggested that a system for using CED needs to be designed that is patient-centric and that exit strategies for medicines under a CED agreement need to be clear for all stakeholders. This includes patients, who should sign consent forms so that they know they are accessing a medicine under a CED agreement, noting

that the medicine could feasibly be delisted if the evidence collected is not persuasive and that it may not be as efficacious as other treatments they could receive. Research data collection infrastructure and governance needs to be developed.

- *Timeliness* - Another issue raised was the time from registration on the ARTG to listing on the PBS. It was suggested that processes need to be streamlined to reduce the time to access. Data show that the biggest delay between registration and funded access happens between the first negative PBAC decision and the final positive PBAC recommendation, which suggests that 'resubmission churn' is the biggest cause of delays. There was a consensus among stakeholders that it was very inefficient to get to an agreed price through using HTA resubmissions as a vehicle for pricing negotiations. Some stakeholders felt that uncertainty was being used specifically to lower the price of new treatments, and that efforts were aimed at eliminating uncertainty rather than concentrating on the plausible case. It was noted that about half of the time delays from registration to eventual reimbursement happens during this period. Around one-third of the time is from a positive PBAC recommendation to PBS listing.

How might current HTA processes be changed?

- *Submission pathways* – Highly Specialised Technologies (including cell and gene therapies) can currently be assessed either through an MSAC or PBAC HTA pathway. It was unclear to stakeholders why this is the case, and it was noted that this can have different implementation issues for the States and Territories.
- *Lifecycle HTA* – It was suggested that HTA needs to be future focused, given the rapid development of technology, and so HTA needs to be done as a continual process as more clinical evidence becomes available.
- *Disruptive technologies* – There was a suggestion that there should be a separate funding pool for technologies that appear promising but that are not yet subsidised e.g., the UK's Cancer Drug Fund. It was also suggested that the system needs to be more harmonised to enable better transitions from pure research funding to clinical trial funding and better transitions between trial funding and formal reimbursement of technologies.
- *Streamlined Commentaries* – It was suggested that there might be ways to focus the commentary on the medicine produced by the independent evaluation groups and, thus, create more efficiencies in the assessment process e.g. when there is not a lot of key clinical data, the evaluators and sponsors may still get caught up on small things in the model which do not really have much bearing on PBAC's decision. Sensitivity analyses may add credibility to the model, even when the clinical data suggests it is not credible. Streamlined commentaries that only document matters likely to impact on decision-making may reduce the time and burden on all involved.

Based on these findings from the stakeholder workshops, and the evidence gathered as part of the scoping review of international HTA pathways, policies and processes, we have suggested some possible ways forward for achieving the goals of the HTA review – Implications, below.

IMPLICATIONS

The evidence obtained on different HTA pathways and processes indicates some variability in approach by different jurisdictions, which is not unexpected given the different health systems and methods of financing that operate internationally. There was no evidence obtained to indicate that one approach was more effective than another. HTA *'globalises the evidence'* but *'localises the decision'* and so each country has developed or adapted pathways and processes suitable for their local context, values and priorities.

A couple of areas of emerging consensus were noted. Many jurisdictions have introduced parallel regulatory/reimbursement processes to speed up access to medicines. For equity reasons they have also introduced funding access programs, such as MAPs and CED, to speed up access for patients with high unmet clinical need and where there are deficiencies in the available evidence base for the technologies that treat them. There is also some agreement on the eligibility criteria for technologies to participate in these funding programs, although no two systems are completely alike.

The published international experience in facilitating swifter access to medicines, vaccines and highly specialised technologies, and discussion with stakeholders from government, industry and evaluation groups, has highlighted areas where change could possibly be made to current Australian HTA pathways, policies and processes in order to address the objectives of the HTA Review.

These objectives are to deliver a comprehensive set of recommendations for reforms to Government that:

1. are implementable and sustainable for both health funders (Commonwealth, state, and territory) and the health technology industry
2. deliver Australians equitable, timely, safe and affordable access to a high-quality and reliable supply of medicines for all Australians
3. adopt a person-centred approach in HTA
4. deliver the outcomes sought by recommendations from the Inquiry that are agreed in principle in the Government Response
5. further the objectives of the new National Medicines Policy
6. ensure HTA policy and methods are well adapted to, and capable of assessing, new technologies that are emerging or are expected to emerge in the coming years, and
7. do not compromise assessment of patient safety, effectiveness and cost, or advice to Government on subsidy of health technologies.

Bearing in mind these objectives, and considering the evidence obtained, three main areas of change are suggested – (1) optimising current approaches, (2) front loading, and (3) HTA pathway transformation.

These suggestions draw from international experience in promoting swifter and more equitable access to medicines, vaccines and highly specialised technologies but also consider what is unique to, and might be feasible for, the Australian context.

OPTIMISING CURRENT APPROACHES

One of the points raised by stakeholders was that PBAC submissions can be streamlined and accelerated using the *current* process where there is a concerted will by all parties. Pathway A was highlighted as a model approach for facilitating swift progress through the system after PBAC has recommended a medicine for PBS listing. Part of the appeal of this pathway is that it is facilitated and involves the Department assigning an individual case manager. This case manager is responsible for shepherding a submission throughout the listing process and provides a single contact for maintaining communication with the sponsor and other stakeholders. If this case management approach was adopted more widely, this would likely require additional staff resourcing or re-deploying within the Department and might therefore be costly. However, Pathway A currently has an appropriate level of cost-recovery and if this case management approach was widened to all medicines undergoing re-submissions – or at the least those medicines for those medicines for which there is high unmet clinical need - it could facilitate swifter PBS listings.

One of the other points mentioned in workshops was that PBAC Commentaries on applicant submissions could become more streamlined such that they basically consist of an executive summary at the beginning and then the technical supporting information is provided in a series of attachments. Although this would reduce the review workload by the appraisal committees (i.e., PBAC and ESC discussants) and the Department, the time taken to develop this document would likely be longer for evaluation groups, as producing a good synthesis takes time. However, if the evaluation period is extended slightly this might be achievable.

One problem with the proposal to produce Streamlined Commentaries for all evaluations is that the current executive summary format has multiple target audiences – it is meant to inform PBAC, the sponsor, and the public (as the executive summary of the Commentary forms the basis of the Public Summary Document). Ideally, to improve the transparency and coherence of communication, there would be one executive summary aimed at the PBAC and the sponsor, with key points identified and justified but written in scientific language; and one Public Summary Document written in plain language and aimed at the public. The latter may be co-developed with patients and both could be made available on the PBAC website. The development of two separate documents would have resource implications in terms of time and expertise – and writing in plain language is a specific skillset that may not reside in the evaluation

groups – but it would improve transparency about the process of evaluating the medicine and the factors that influenced PBAC decision-making.

This approach would improve the transparency of the HTA process and support more effective patient engagement, particularly when combined with clearer guidance on the kind of patient information that is valuable for the separate assessment and appraisal (decision-making) elements of HTA [130]. Adequately resourcing patient engagement (e.g., with government funds and through the co-design of an enhanced consumer engagement process) stands as a potential means of improving patient engagement in the Australian HTA process.

FRONT LOADING

The elements suggested for this domain draw on the information obtained on 'proactive' or hybrid HTA processes, the conclusions from papers 2 and 3, along with some points raised in the workshops. Mechanisms for monitoring emerging technologies and for determining the clinical place for medicines and technologies *before* they are submitted could facilitate swifter progress of a submission or funding application through the evaluation and appraisal process and allow greater stakeholder engagement.

An active horizon scanning process targeting 'disruptive' technologies (whether they are medicines, codependent technologies, or highly specialised therapies) could act as a feeder to HTA evaluations, either through the production of horizon scanning reports or 'proactive HTAs' (depending on the level of information available), to inform policy planning and funding decisions. It could also involve identifying potential new patient indications for the 'repurposing' of medicines and technologies. This could trigger government negotiations with industry, patient groups and/or clinical professional societies to sponsor the proposed new indication.

International collaboration could help with horizon scanning, but the aim would be to have a seamless integration with current HTA activity so that as new information emerges on 'disruptive' technologies an existing HTA report and economic model can be updated – as a *living HTA* process that provides an ongoing analysis to inform preparedness and policy decisions. This type of 'living HTA' report, produced as part of a lifecycle approach to technology assessment and appraisal, could not be done for *every* medicine or technology coming through the health system, simply due to the sheer resourcing that would be required. This type of living approach is also not generally needed for most medicines as funding decisions are usually clear cut and the decision, and any new evidence, is reviewed at resubmission (if the medicine is not funded) or as part of a post-market review (if funded). It is only where there is an urgent need for the medicine, and the decision is uncertain, that a 'living HTA' might have value as part of a coverage with evidence development program (see further discussion on this below).

In addition to proactive horizon scanning and integration of it with the HTA process, another element of front loading the HTA process could be to undertake a PICO[4] confirmation for first-in-class medicines/highly specialised technologies that have plausible significant clinical benefit. First-in-class medicines or technologies are suggested because they are most often those technologies that might prove to be disruptive and are also the least likely to have a clearly defined place in clinical practice. In addition, once a clinical pathway has been developed for a first-in-class medicine or technology then subsequent similar treatments will likely find a place within the defined pathway. When there are many treatments within the class the whole category can be reviewed using the current post-market review process.

As mentioned in paper 3, there is always a possibility that adding in an additional PICO process for first-in-class medicines with plausible significant added therapeutic value, like for codependent technologies, will slow down the process overall because the PICO confirmation might need to be reviewed by the PICO Advisory SubCommittee (PASC). Front loading this process could, however, reduce resubmissions that are rejected because of concerns with the population and comparator – which is more likely to occur with first-in-class medicines and technologies. Alternative processes for confirmation of the PICO could also be created that do not involve the formal review by a PASC-like committee, and so reduce the length of the time taken e.g., public consultation feedback going directly to Departmental medical officers and evaluation groups for incorporation into a PICO confirmation document, or the development of a PICO by sponsors for discussion at PBAC pre-lodgement meetings. If a public consultation process is undertaken for the PICO and advice is provided to the sponsor (or, alternatively the evaluation groups if they are developing it) on the correct elements of the PICO, there might be a question over the status of that advice i.e., whether it is binding or non-binding advice for the development of the submission to PBAC. Status as 'non-binding advice' might be preferable if the time frame between development and the submission is lengthy, given that near-market comparators may emerge and/or new clinical trials might report in the interim. However, for the process to be useful and reduce 'resubmission churn' it would be helpful if departures from the non-binding advice were the exception rather than the norm.

TRANSFORMING THE CURRENT HTA PATHWAY FOR MEDICINES AND TECHNOLOGIES

Highly specialised technologies

While it might be more predictable and equitable for all highly specialised technologies to go through a single HTA pathway, it would also likely require amendments to be made

[4] Population, Intervention, Comparator, Outcome

to legislation concerning PBAC's remit or to the current (2020 – 2025) *National Health Reform Agreement* (NHRA) [214].

The elements of the NHRA governance process for highly specialised technologies that relate to the HTA pathway are reproduced below (noting that the COAG Health Council has since been replaced/renamed):

A. The Medical Services Advisory Committee (MSAC) and Pharmaceutical Benefits Advisory Committee (PBAC) Chairs, together with a COAG Health Council (CHC) representative will jointly decide on which committee should assess the application for a new drug or therapy, where the HCT *[high cost, highly specialised therapy]* is likely to be delivered in a public facility.

> I. The rules for PBAC assessment are set out in the National Health Act 1953. Where the matter does not fall within the definition for consideration by PBAC it is assessed by MSAC.
>
> II. The Chair of COAG Health Council will nominate one representative on behalf of all states and territories to participate in this meeting. This representative is to have the same clinical expertise as the MSAC and PBAC Chairs.

B. For therapies that will be assessed by MSAC and delivered in a public hospital, the Commonwealth will write to states and territories advising them that an application has been received and invite them to make a submission to MSAC for consideration, noting that the states and territories will need to abide by the same confidentiality requirements as MSAC members.

> I. The terms of reference of MSAC will be amended to ensure that MSAC is obliged to consider any submission from a state or territory where it is relevant to comparative safety, clinical effectiveness and/or cost-effectiveness of the therapy.

It is apparent that some highly specialised technologies, including cell and gene therapies, have been progressed through the MSAC evaluation and appraisal pathway because they are technologies that would be administered in a public facility. Those that do not require administration in a public facility might meet the criteria for review by PBAC. In the absence of changes to the remit of PBAC or changes to the NHRA requirements for highly specialised technologies, at minimum a clear communication strategy could be employed so that there is transparency around the current process for selecting whether MSAC or PBAC reviews a particular highly specialised technology, and that the States and Territories are notified of this.

Introducing a model validation process

A consistent theme and source of frustration that emerged from stakeholder workshops was that the current PBAC HTA process had become a mechanism for price negotiation. This was described as industry providing multiple sequential submissions for evaluation

to reduce decision uncertainty and arrive at a cost-effective price for the medicine. This "resubmission churn" can result in lengthy delays until a PBS listing is recommended by PBAC.

A method of reducing "resubmission churn" (i.e., reducing 'formal' resubmissions and ensuing delays) that was considered was the use of an independent price negotiation body, as has been suggested in public consultation submissions. The previous Pharmaceutical Benefits Pricing Authority used to provide such a function but was found to essentially duplicate the activities of the PBAC. If such a body was re-established it would mean that decisions would be made without detailed knowledge of the submission and the economic model that underpins the determination of cost-effectiveness, and which allows the PBAC to fulfil its legislative remit to recommend for listing those medicines that are deemed cost-effective.

One possible alternative would be to undertake an ongoing model validation process that occurs outside the 17-week PBAC assessment and appraisal cycle and would last for up to 12 months.

This alternative process would only be triggered if the medicine was considered to have added therapeutic value, *and was provisionally PBS listed on that basis*, but where there was decision uncertainty related to the economic model/price. This model validation would be an alternative to using PBAC decision-making as a mechanism for price negotiation.

The process would be initiated when PBAC considers that a medicine has uncertain or unproven cost-effectiveness (but has clear added therapeutic value). Instead of a rejection and a formal resubmission, an iterative model validation process would be triggered. The relevant ESC discussants, evaluators, Departmental staff and the sponsor would meet and work iteratively towards reducing uncertainty in the economic model assumptions and inputs in line with the advice from PBAC. This would occur essentially outside the 17-week assessment and appraisal cycle until such a point that a modified resubmission can be formally lodged and be reconsidered either by the full PBAC or the PBAC Executive (see Figure 14). If the model uncertainties have been resolved and the remaining contributor to likely poor cost-effectiveness is simply the price, then there would be scope for direct negotiation between the sponsor and the Department on price before the model is resubmitted to PBAC for a decision. As the Department represents the taxpayer, subsidises the various medicines and technologies through the PBS and MBS, and works within a constrained budget, their willingness-to-pay must be canvassed as part of the HTA process. If the model cannot be successfully validated and PBAC decides to reject the submission – even after the concentrated effort undertaken - then pricing policies and approaches to financial clawback for funding by the taxpayer would be triggered (and may include refunding and delisting of the medicine or the adoption of a fallback price), noting that the medicine was *provisionally* PBS listed. The type of 'clawback' mechanisms triggered would be informed by Paper 6 of the HTA Review.

Risks associated with this approach primarily relate to introducing less objectivity into the assessment and appraisal process. This could be mitigated by ensuring probity guidelines are followed. Another risk is that the iterative process used for this validation process could tie up resources that would be needed for the typical PBAC 17-week assessment and appraisal cycle. It would, therefore, be prudent to place a cap on the duration of the model validation phase. The greatest risk to Government of this approach is the possible public/patient and media response, and potentially legal cases brought by sponsors, should a medicine be de-listed after it was provisionally PBS listed. One approach to minimise this risk could be the use of an agreed minimum fallback price if a model is not validated, at least until a subsequent resubmission is produced and validated.

Benefits of the model validation approach would be:

- Instead of resubmissions occurring multiple times over an extended period, the evaluation process would be concentrated in one ongoing iterative feedback loop. This would lead to a reduced number of resubmissions, and a consequent reduction in the labour required in each 17-week cycle to produce and review Commentaries (some of which would be diverted to the 'model validation' process).
- With a reduction in the number of resubmissions the full 8.5 weeks in the current PBAC evaluation cycle can be utilised for producing a Commentary, potentially improving the quality, synthesis and rigour of these documents i.e., only having one internal deadline at 8.5 weeks, not deadlines at the 5 week and 8.5 week time points.
- As a provisional listing would occur contingent upon a decision of added therapeutic value, the delay currently associated with resubmissions, and particularly the inability of resubmissions to be submitted in the subsequent 17-week PBAC cycle, would be removed. The time until a positive PBAC recommendation (albeit provisional) could, therefore, be accelerated.

We did investigate whether this process could be incorporated into the evaluation "off cycle" i.e., after the Economic subcommittee has reviewed the submission but prior to PBAC consideration, but the timeline available was not sufficient within the current 17 week cycles. To increase the time between ESC and PBAC, we considered permitting the sponsor to delay PBAC deliberation to a subsequent PBAC meeting. However, this results in a substantial delay (i.e., an additional 17 weeks). We therefore considered the possibility of increasing the frequency of PBAC meetings (two overlapping cycles), to permit an option to extend evaluation time and permit sponsors to address concerns raised by ESC prior to PBAC. This would have the effect of adding approximately 8-9 weeks to the available evaluation time (see Figure 13).

To incorporate this additional time, the typical evaluation cycle time (to create the Commentary) would need to decrease. This would not be feasible as PBAC's evaluation groups consistently stated at the stakeholder workshops that the current time period

for evaluation is insufficient. In addition, management complexity would increase due to the need for additional resourcing of external HTA evaluation staff and internal Departmental staff to be able to manage the overlapping cycles. In addition, having this activity undertaken pre-PBAC decisions means that it would not be possible to work to resolve issues formally identified by the decision-maker.

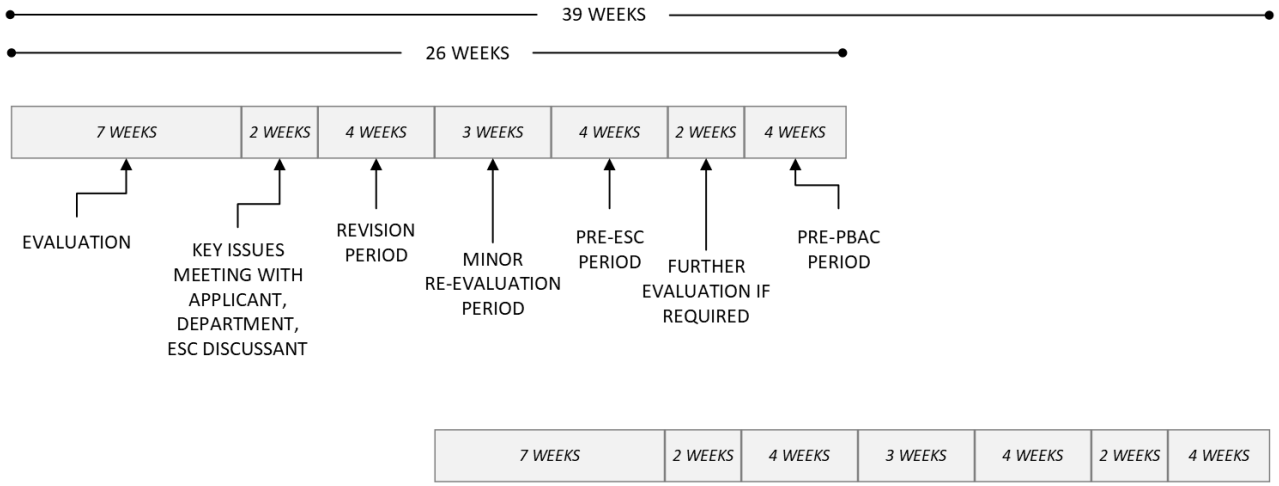


Figure 13 Pre-ESC model validation process that was considered and rejected

Meeting frequency and evaluation timelines

One way of accelerating PBAC decision-making and PBS listings could be through having additional meetings and introducing overlapping PBAC cycles. More meetings would reduce the load on discussants at individual meetings, and this would be further reduced if the model validation approach, mentioned above, was instituted because there would likely be fewer resubmissions. There are, however, a few practical concerns with having overlapping PBAC cycles, mainly relating to: (1) the availability of, and burden on, a small number of experts who are members of PBAC and its subcommittees, (2) the availability of evaluators across multiple overlapping cycles, (3) the ability of sponsors to produce submissions across multiple overlapping cycles, and (4) the administration and cost of maintaining multiple submissions points and overlapping cycles.

Given this, it might be a more reasonable approach to have the PBAC Executive take on more decision-making responsibility. For example, if the model validation approach mentioned above was introduced it might be reasonable to have the finalised resubmission either go to the full PBAC committee (skipping ESC, as the ESC discussant will have been part of the model validation process) within the usual cycle *or* allow it to be considered outside the cycle by the PBAC Executive. The PBAC Executive already meets regularly. There are three full PBAC meetings per year, so if three PBAC Executive meetings per year were also responsible for deciding whether the model had been validated or not, then listing decisions (whether confirmatory or provisional) could be made every two months, rather than every four months as occurs currently.

Developing a Risk-calibrated Rapid Access HTA Pathway

Anticipatory funding mechanisms for all medicines and disease areas

Several health systems have HTA pathways that deliver faster access of medicines to patients, whether for the whole population or for specific patient groups that are disadvantaged as part of the usual HTA processes.

There are many systems, like Australia, that have a formal HTA framework that examines the value of a health technology to society before it is funded by the taxpayer. A few countries have HTA pathways that subsidise technologies in anticipation of them being suitable for funding. That is, the technologies are subsidised either at market authorisation or post-market authorisation but prior to a deliberation on cost-effectiveness or value for money.

The benefit of these anticipatory subsidisation processes is that patients can get swifter access to the technology, and the potential health gains in terms of length and/or quality of life. This has flow on benefits to their carers, family members, the economy and society. Another benefit is that there is potentially more equitable access to technologies among specific population subgroups that are typically disadvantaged by current HTA processes.

The likely risks and risk mitigation strategies depend on the anticipatory funding mechanism that is employed. For systems that subsidise technologies at market authorisation, without – or with a delayed - HTA assessment and appraisal, the risk is that a new treatment is funded that is not *comparatively* safe, effective, or cost-effective relative to standard medical management for that condition in the health system. Part of the reason for this is that the types of decisions made by regulators and HTA/payers differ. Regulators need to make a simple qualitative decision as to whether the clinical benefits outweigh the risks of the treatment to the individual. This contrasts with the HTA agency or payer perspective which is about making a quantitative decision on the *magnitude* of clinical benefit *or added therapeutic value* of the new treatment compared to the best available therapies. Thus, the HTA/payer perspective is about whether there is sufficient value demonstrated by the outcomes reported in the evidence dossier to spend taxpayer funds on the treatment in question, as opposed to spending it in other areas of the health system that are equally in need. The HTA/payer perspective considers the opportunity cost of the decision. If too many medicines are funded at market entry that are not-cost-effective it means - even if the price is later re-set - that those funds cannot be spent on other areas of the health system, potentially threatening the system's sustainability.

Funding technologies as soon as they are approved by the regulator, also means that there is a potential health risk to patients if the comparator selected for the regulator is not the same as used as standard medical management. Patients may be receiving substandard care with the new treatment when compared with the treatment that they would have ordinarily received. The opportunity cost of funding that new treatment

means that other better or more cost-effective treatments also cannot be funded (noting budgetary constraints to decision-making).

A way of mitigating the clinical and economic risk is to have an HTA evaluation undertaken prior to, or at the same time as, market authorisation (as per Australia's parallel TGA/PBAC process). Australia is a leading exponent of this approach, with PBAC typically making its initial funding decision (at least for cancer medicines) 17 weeks prior to listing of medicines on the Australian Register of Therapeutic Goods [59]. The problem is that nearly two-thirds of PBAC decisions concerning the initial submission are negative. Uncertain cost-effectiveness is one of the main reasons - and so a cycle of resubmissions commences, delaying patient access to the medicines. It should, however, be noted that most of those medicines considered to have added therapeutic value are eventually subsidised.

A way of mitigating the opportunity cost risk to government/the payer of an anticipatory funding mechanism is to have some sort of refund, rebate or price penalty agreed between the payer and the sponsor at PBS listing so that the money spent can be clawed back if the technology fails to live up to the clinical benefits and value for money that was anticipated. The money could be quarantined to fund horizon scanning activity for disruptive technologies or to identify candidates for proactive HTA, e.g., medicine repurposing (as suggested in Paper 2) or for some other reason.

Added therapeutic value

Added therapeutic value is a concept that does not have a universal definition, mainly because value is measured by international HTA agencies in various ways. As added therapeutic value is an important concept for funding decision-making and for the development of HTA pathways, we developed a working definition of the concept for Australia which took into account the obligations of the PBAC under the *National Health Act 1953* and which also considered how other HTA agencies define the concept.

Section 101 of the *National Health Act 1953* states, with reference to PBAC (underline added):

(3A) For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations.

(3B) Without limiting the generality of subsection (3A), where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee:

> (a) shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies; and
>
> (b) if the Committee does recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part, the Committee shall include in its recommendation a statement that the Committee is satisfied as mentioned in paragraph (a).

Therefore, added therapeutic value could be considered by the *Act* as significant improvements in efficacy or reduction of toxicity over the alternative therapy or therapies. Given the guidance in the PBAC Guidelines, we have clarified this concept to ensure it relates to clinically meaningful improvements in population health outcomes.

Population health outcomes was mentioned because the effects of a medicine might not be limited to the individual patient. For example, for some medicines there are potential impacts on the health of carers, vaccines can impact on herd immunity and protect the community from disease, and antimicrobial agents, if stewarded appropriately, can reduce the circulation of resistant microbial strains having broader impacts on the health of the community.

The full working definition used was:

Added therapeutic value *– A significant[1] improvement in population health outcomes obtained with a new medicine or technology when compared to the best available therapeutic alternatives.*

[1]'Significant' means a clinically important improvement in health outcomes. It is not demonstrated solely by a statistically significant difference in health outcomes.

This definition is used for the proposed Risk-calibrated Rapid Access HTA Pathway provided further below.

Conditional funding mechanisms for selected medicines and disease areas

Many jurisdictions in the evidence base fund technologies at market authorisation or post-market authorisation through managed access agreements or pathways because they show promise of addressing unmet clinical need for rare diseases or severe/life threatening disease, but the evidence base is too immature to demonstrate this. Like the situation above, the risk with this type of anticipatory funding is that the promise of the technology might not be realised or is never known with certainty. Meaning that patients may be receiving substandard care and/or the funding could have been better spent elsewhere.

As has been demonstrated by several international HTA systems with managed access agreements, Coverage with Evidence Development (CED) in some form is likely to be beneficial if applied to high priority disease areas where there is unmet clinical need,

where the technology shows promise but there is limited evidence available demonstrating that (or likely to demonstrate that), and where the added therapeutic value and cost-effectiveness are uncertain.

A clear definition of high unmet clinical need and a prioritisation process that targets treatments in priority disease areas would be crucial to the success of any such CED program. These criteria would need to be developed by government, in consultation with stakeholders, prior to implementation. Additionally, there should be clear expectations around the development of evidence to confirm (or not) the promise of the treatment, with policy makers, sponsors, academics, economists, clinicians, patients and HTA evaluators advising on how data should be collected and interpreted.

This data could be obtained from a confirmatory trial that is underway or could be 'real word evidence of effectiveness' (RWEE) – essentially observational studies. Real world data are used in many aspects of HTA but are rarely used for assessing the clinical safety and effectiveness of a medicine because – given these are primarily observational data – there are biases and/or confounding impacting the internal validity of the data due to the way the data have been collected and the way the health outcomes have been measured. However, for some rare diseases or conditions, randomised trials are unable to be performed and so less reliable evidence gathering mechanisms may need to be considered.

One thing to note is that with RWEE *any increment in clinical benefit is likely to be reduced* when compared to a randomised trial because those patients selected for a trial are usually those with the greatest capacity to respond i.e., without comorbidities, the 'healthy sick' and, being in a trial, are motivated to comply with the treatment protocol. If a medicine participates in a CED process it is therefore unlikely that a price *increase* would be justified based on RWEE data. For the most part, negotiated prices would remain the same or be reduced following the provision of confirmatory evidence.

Data collection architecture for RWEE would need to be invested in and systems would need to be user friendly, interoperable and with minimal burden on the front-line health care professionals who would likely be responsible for data entry. Paper 7 may provide additional information on the characteristics of such data collection systems. Data are most likely to be trusted if held either independently or by government. Sponsors would need to pay for data collection, as they would for a randomised trial, so that perverse incentives are not created i.e., to have government collect data rather than industry conduct the trials. This would also make it more equitable, such that sponsors of orphan drugs have similar R&D trial/study requirements, as sponsors of treatments for more common conditions.

Where confirmatory trials are pending, funded access through CED programs should not be implemented immediately if local trial recruitment is likely to be affected. The recently released *Monash Cancer Surrogate Report* for PBAC [215] found that the vast majority of 'final' trial findings for cancer drugs provided overall survival results that were consistent with the first 'interim' results presented, strengthening the case for

some sort of CED process to be implemented for submissions for medicines addressing high unmet clinical need that are awaiting confirmatory trial evidence. These findings imply that either subsequent findings are no better, or that if trial results are worse, they are often not presented. There was only 1 trial that had better final trial results out of 101 trials. This suggests that if clinical benefits are greater than expected from interim findings then a new price request would almost certainly require a new application to the PBAC.

If a CED process is implemented, to mitigate the impact of opportunity costs to the health system of anticipatory funding, there should be consequences if expectations around evidence development or potential benefit are not met. This could involve clawback provisions on price and managed exit criteria i.e., clear agreed rules on how government will disinvest from a treatment found to have no added therapeutic value.

For ethical reasons, an 'opt in' and informed patient consenting process would need to be considered, and appropriate ethical governance, noting that for CED the comparative safety and effectiveness of the medicine at funded access would be uncertain. In addition, there is always the possibility that patients could be responding to a medicine which is subsequently withdrawn [216].

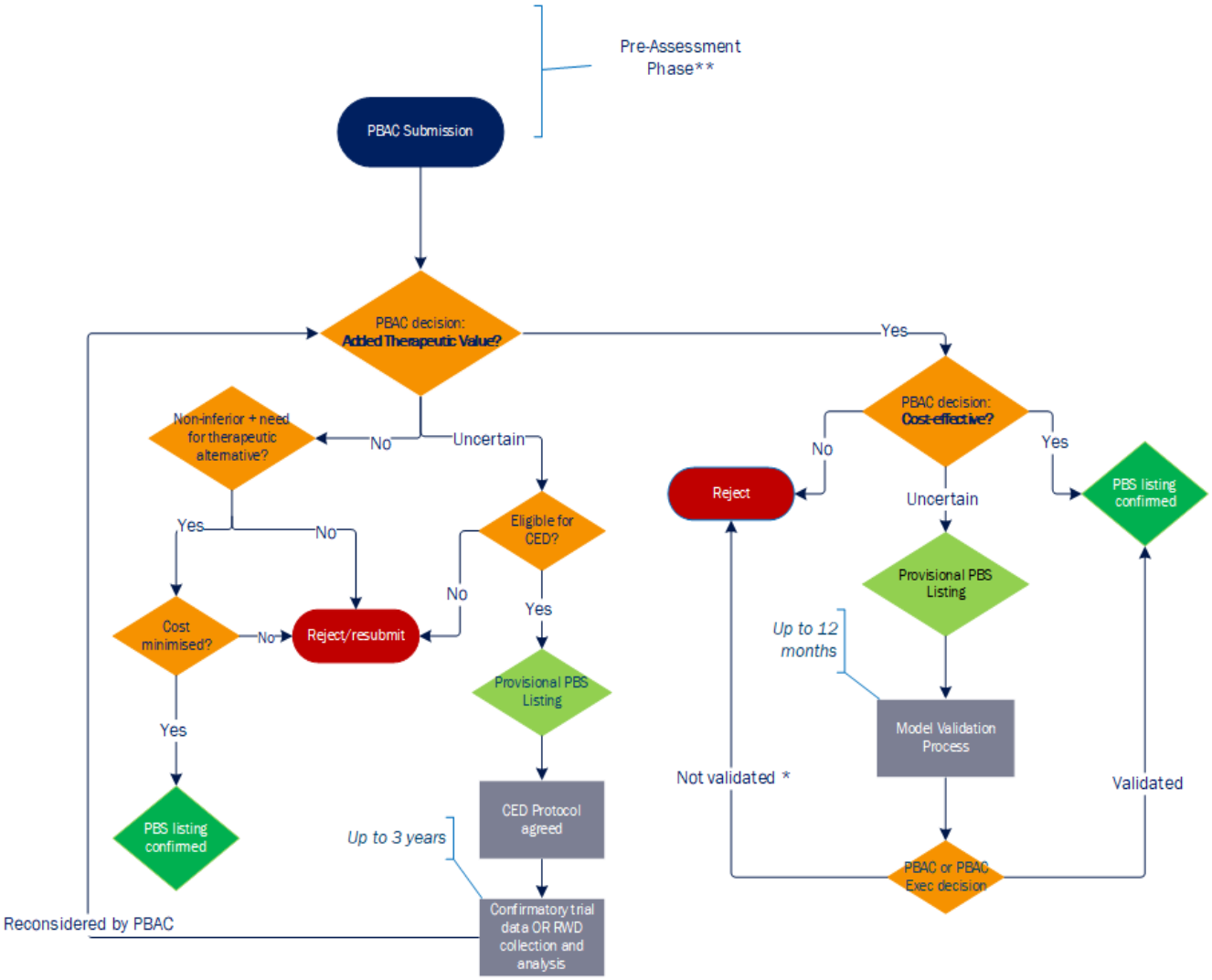
As mentioned in Paper 3, processes should be put in place in a CED scheme to make it clear to patients/carers that the clinical effectiveness and cost-effectiveness of the conditionally approved medicine have not been established, so that they can make an informed decision about using them. Governments and HTA groups may be well placed to provide information resources on these matters, although traditionally issues of informed consent and clinical advice are – and should remain - within the remit of the treating clinician. Questions concerning whether patients would be willing to provide their data to participate in a CED scheme would also need to be addressed [216]. There are also ethical questions about removing access to medicines that have been provisionally funded and are clinically effective (to some extent) for the individual but turn out to be cost-*in*effective at a population level. In these circumstances it is not an appropriate use of taxpayer funds to continue funding the medicine, given the opportunity costs. That is, the funds could perhaps have greater value in maximising population health outcomes if they were spent elsewhere. In these circumstances the role of the medicine sponsor in funding these "responder" patients would need to be considered as, if the full evidence had been presented prior to reimbursement, patients would not have received funded access to the medicine at all. Further information on the ethical implications of a CED arrangement within the Australian health system is given in the publication by Carter, Merlin and Hunter (2023)[216].There is also a risk with CED schemes that the evidence generated will not reduce the uncertainty, and that further evaluation will not be able to establish the benefit/harm profile and cost-effectiveness of the medicine. It is important then that expectations on how effectiveness and cost-effectiveness will be measured (based on the data collected) are defined upfront and agreed in writing by all relevant stakeholders.

Integrating elements into one pathway

One possible approach to balancing the benefits of rapid access to health technologies with safeguards for patients and the economic viability of the system, is to create an HTA pathway that triages the assessment and appraisal approach according to risk. Such a pathway would be flexible enough to change the time point for a PBAC funding decision, depending on the level of uncertainty, and thus the associated risk of an incorrect decision. It would, however, retain a large element of its predictability by having defined timings for submission, assessment and appraisal. This pathway would essentially involve five decision options:

1. On balance the medicine is comparatively safe and clinically effective (the additional therapeutic benefit is of value) and it is cost-effective – **confirmed PBS listing decision**
2. On balance the medicine is comparatively safe and clinically effective (it is non-inferior and an alternative therapeutic option is needed) and it is priced similarly to the comparator (cost-minimised) – **confirmed PBS listing decision**
3. On balance the medicine is comparatively safe and clinically effective (the additional therapeutic benefit is of value) but its cost-effectiveness is uncertain – **provisional PBS listing** with confirmatory listing contingent on a *model validation process* being undertaken to ascertain cost-effectiveness (as per 6.3.1 Introducing a model validation process). Such a process would require a safety net of clawback provisions on price and/or managed exit criteria if cost-effectiveness cannot be demonstrated, given that PBAC has a legislated mandate to ensure that a PBS listed medicine is cost-effective.
4. On balance the medicine is likely comparatively safe and clinically effective (although the magnitude or value of the benefit is uncertain) and its cost-effectiveness is uncertain – **provisional PBS listing** contingent on *coverage with evidence development*, with clawback provisions on price, managed exit criteria, patient consenting process and agreed data collection/interpretation protocol. Medicines eligible for this pathway would likely need to address unmet clinical need (no alternative treatment options), target patients with rare and/or severe or life-threatening disease, and/or demonstrate that a controlled trial or study could not be conducted in a timely way or would not be feasible.
5. On balance the medicine is not comparatively safe, clinically effective and/or cost-effective – **medicine is rejected**.

Figure 14 provides a depiction of these decisions in a proposed Risk-calibrated Rapid Access HTA Pathway.



* Activate clawback provision on provisional listing. Possibly used to fund Horizon Scanning and proactive HTA, given cost-recovery for submission process is already built-in to the existing PBAC submission process.

** Could include PICO scoping phase for first-in-class, potentially disruptive, medicines and technologies.

Added therapeutic value is defined as a significant[1] improvement in population health outcomes obtained with a new medicine or technology when compared to the best available therapeutic alternatives.

[1] 'Significant' means a clinically important improvement in health outcomes. It is not demonstrated solely by a statistically significant difference in health outcomes.

Figure 14 Risk-calibrated Rapid Access HTA Pathway for PBAC submissions

A summary of the risks and benefits associated with this proposed pathway is given in Table 9.

Table 9 Risks and benefits associated with Risk-calibrated Rapid Access HTA Pathway option

Stakeholder	Risk	Benefit
Evaluators	Difficulty with staff resourcing and management given co-existence of 17-week cycle and model validation process	More time to evaluate submissions (increase in quality, synthesis, and rigour) Consistency in evaluation (same evaluators seeing medicine through the validation stage)
Sponsors	Difficulty with staff resourcing and management given co-existence of 17-week cycle and model validation process Risks associated with financial clawback mechanism (depending on type) given model validation might not be achieved	Earlier access to market and potentially increased sales Greater throughput of products through the HTA system
Payer/ Government	Difficulty with staff resourcing and management given co-existence of 17-week cycle and model validation process Depending on clawback mechanism employed, possible public/media and legal challenge for de-listing decisions	Earlier patient access to medicines leading to potential downstream cost savings to the health system and improved public health. Reduced 'resubmission churn' potentially freeing up resources. Addressing public concerns regarding swifter access to medicines and patient-centricity of the HTA evaluation and appraisal process Australia may become a tier 1 market again with more sponsors being willing to launch products
Patients/ Clinicians	Responders to a medicine might find it is subsequently de-listed by Government or withdrawn by the sponsor if model not validated and fallback price is not commercially viable (despite being pre-agreed at listing).	Earlier patient access to medicines leading to improved public health. More equitable access for people suffering from rare diseases and conditions Potential increase in throughput of funded medicines and technologies being available on the market if Australia becomes a tier 1 market

Elements of this HTA Pathway could be introduced as stand-alone processes and/or introduced in a staged fashion. For medicines undergoing the parallel process that is currently undertaken between TGA and PBAC, this Pathway would essentially mean that medicines are *PBS listed at market entry* if found to be of added therapeutic value or eligible for CED by the PBAC. Medicines undergoing the sequential (regulation followed by HTA) process would be funded earlier than currently. The model validation process would reduce 'resubmission churn' and also speed up the time to PBS listing and patient access to medicines. Orphan drugs for rare diseases with a scant evidence base could be funded while data on performance are obtained in an ongoing fashion. As in the current process, non-inferior medicines can be cost-minimised against a comparator and PBS listed to ensure the supply of therapeutic alternatives in the event of medicine shortages.

The Risk-calibrated Rapid Access HTA Pathway picks up elements of some of the swifter evaluation and appraisal pathways used overseas but adapts these to the unique Australian context. This Pathway addresses the objectives of the HTA Review, is patient-centric, equitable, transparent, balances speed with rigour and aims to keep the Australian health system sustainable.

Paper 2: Horizon scanning and early assessment

Health Technology Assessment Policy and Methods Review Papers

March 2024

Horizon scanning and early assessment

Paper 2 in Health Technology Assessment Policy and Methods Review Papers

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Acknowledgements

We would like to thank the following people who took the time to provide assistance and/or fact checked the information included in this paper –

Dr Izzuna Ghazali, Public Health Physician/Deputy Director Malaysian Health Technology Assessment Section (MaHTAS)

Dr Lesley Dunfield, Senior Advisor, Partnerships, at the Canadian Agency for Drugs and Technologies in Health (CADTH)

Ms Linda Mundy, formerly of the HealthPACT secretariat.

Ms Lydia Loke, Lead Specialist, Drug and Vaccine Evaluation, Agency for Care Effectiveness (ACE), Singapore Ministry of Health, Singapore

Dr Alric Ruether, Head of International Affairs, and Irene Urbina of the Institute for Quality and Efficiency in Health Care (IQWiG), Germany

The Department of Health and Aged Care project staff who coordinated the HTA Review and worked with AHTA on delivering each of the papers.

The HTA Policy and Methods Review Reference Committee for feedback and guidance throughout the project.

SCOPE OF RESEARCH

The research topics for Paper 2 are outlined in the Research Topic section and summarised below.

The objective of Paper 2 was to compare the Australian approaches for horizon scanning for emerging health technologies and early assessment of new health technologies with those that are used internationally. The characteristics of interest in these processes and methods included the governance or processes, involvement of stakeholders, the application of information gathered during horizon scanning and the applicability of identified approaches to the Australian setting. Paper 2 also examined how technologies were selected for early assessment, the methodology used for assessment, and, whether and how equity considerations were included.

SUMMARY OF FINDINGS

This paper provides information about HTA activities that generally occur at earlier stages in the technology lifecycle than traditional HTA (such as occurs to inform the Pharmaceutical Benefits Advisory Committee, PBAC). These activities fall into two main categories:

- horizon scanning
- early assessment

Horizon scanning is an activity which aims to identify new and emerging technologies that have the potential to impact on the provision of healthcare. It usually occurs between one and three years before the technology will become available in a health system.

The nomenclature and definitions of early assessment varied widely in the literature. We have described the reported research and processes of horizon scanning and early assessment, according to their purpose and timing. Horizon scanning is primarily undertaken for health system planning and preparedness, whereas early assessment aims to provide information to inform medicine development and diffusion at different stages of the lifecycle. This paper considers three types of early assessment: early value proposition, early scientific advice, and early value assessment. Figure E1 shows the approximate timing of these types of technology assessment along the product development lifecycle.

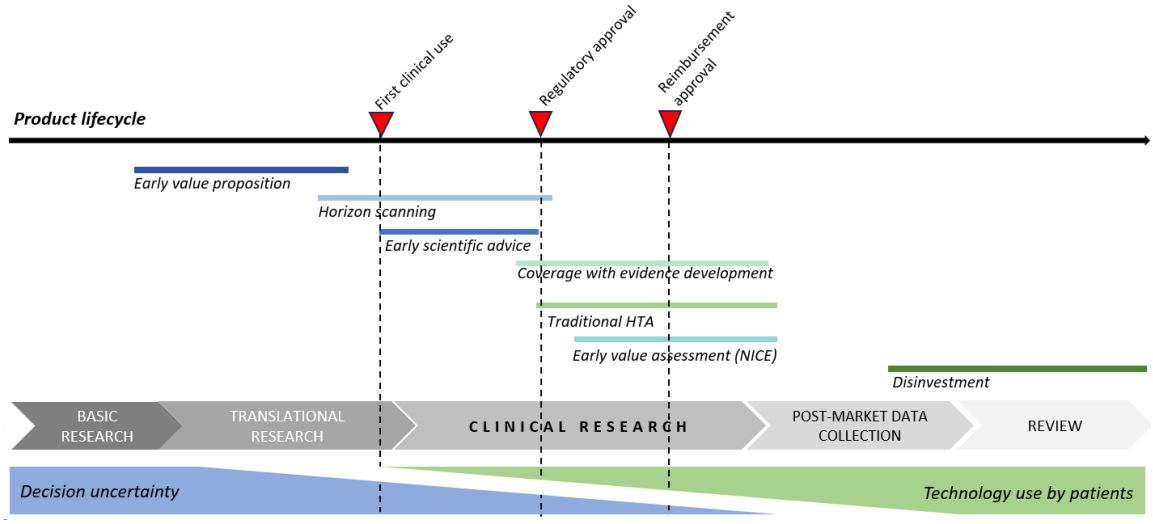

Figure E1 Types and timing of assessment and research in the technology lifecycle

Source: This figure was constructed using input from [217-219]

Note: Traditional HTA can encompass parallel processing i.e., the HTA process can start prior to regulatory approval but still uses similar methods to those usually employed after regulatory approval. HTA may also occur after reimbursement approval if reassessment is indicated.

HORIZON SCANNING

Horizon Scanning (HS) for medicines (and sometimes vaccines) is undertaken by a small number of HTA agencies around the world. Systems are well developed in Canada (CADTH), the USA (ECRI/PCORI), the UK, and in some European countries. There are several inter-agency and cross-country collaborations in Europe and other regions. Recently the Australian Government Department of Health and Aged Care ('the Department') has entered a formal collaboration with seven international HTA agencies (AUSCANZUK), with the goal of working towards new shared approaches to HTA. The partnership has prioritised HS, and currently there are activities underway to develop procedures for information and resource sharing on non-pharmaceutical technologies.[5]

There are a number of motivations behind HS collaboration, but one of the primary reasons is to share resources as the HS process can be resource intensive. Some countries manage the resource intensiveness by limiting the scope of their HS program. Collaboration can only be undertaken successfully if there is alignment between the participating jurisdictions in the goals or purpose of the HS. There may be differences in the populations and technologies targeted, time horizons (short, medium, long term), and purpose.

For most agencies, HS follows a process of topic identification, filtration of topics, and selection (prioritisation) of topics for further attention. Some systems differ in how intelligence is gathered on the topics, particularly the use of automated digital systems, and in the dissemination of findings. Methods for patient engagement are primarily included in the largest and most established HS organisations (i-HTS, CADTH and NICE).

HS for vaccines can be included in the general HS process for medicines or run parallel in a separate pathway. Some jurisdictions run HS for vaccines as a separate process initiated by government or expert committees, and some use formal or informal early advice to inform the process.

None of the research identified provided any information on the impact of horizon scanning on health systems, and whether it achieves its goal of allowing planning and preparation for technologies emerging into the health system.

EARLY ASSESSMENT

Early assessment was subcategorised into three forms – early value proposition, early scientific advice and coverage with evidence development, with early value assessment (EVA) as an example of the latter. These three forms of early assessment occur at various timepoints in the early part of the technology lifecycle, from prototype through to regulatory approval.

Early value proposition (EVP) is a term we have coined for a concept often misnamed as 'early HTA'. EVP is a concept that relates most commonly to economic analysis performed early in a technology's lifecycle – 'as early as' it is feasible. Latterly, other aspects to determine value have been included in these early analyses, such as stakeholder preferences. The aim of these studies is to inform investment and product development decisions for the technology

company. They do not, however, typically inform decision-making by policy makers i.e., to promote an equitable, efficient and high-quality health system, and so do not align with the accepted definition of HTA. The intelligence provided by this type of analysis is largely of use only to the company.

Early scientific advice (ESA) is available to medicine developers across many jurisdictions and countries, and is provided by regulatory and HTA agencies, sometimes in tandem. Most commonly it involves advice provided to the company before the commencement of a key trial, to advise on aspects of trial design and on the population, intervention, comparator and outcomes (PICO) that are of relevance to HTA decision-making. Although this advice is most advantageous to the company, there is also scope for patients to have input into trial design and the outcomes chosen, to ensure any data obtained are meaningful to them. Limited evidence suggests that ESA may result in faster access to medicines, and this benefits patients. Whether ESA provides additional value to the process of HTA (through a reduction in uncertainty) is unknown as no research evidence was identified that objectively evaluated its benefits.

Coverage with evidence development can occur pre- or post-market authorisation of a health technology. An example of the latter is EVA, a process recently initiated by NICE in the UK. This scheme represents an access pathway for medical technologies (not medicines) and is strongly scaffolded by clinical needs and wider health system priorities. Whilst it is difficult to see the applicability of this process to medicines in Australia, except perhaps for rare diseases, there are certainly elements that would apply to the HTA of other types of medical technologies, such as highly specialised technologies (e.g., cell and gene therapies). Other coverage with evidence development schemes are discussed in more detail in papers 4, 8 and 9 of the HTA Review.

IMPLICATIONS

Australia currently has no HS for medicines and re-introducing it would need to be carefully considered in light of the resources required and how the results would be utilised. Ways of addressing these issues for HS are being considered by the AUSNZCANUK international collaboration the Department is now partnered with. There is, however, a key piece of information that is missing from the available research on HS – and that is whether and how HS impacts on the health system and results in greater preparedness for emerging technologies.

In the absence of this information, for HS to be useful in Australia, there would need to be clear guidance on how the information will be used to action health system preparedness for new medicines, noting that Australia currently has a medicines and vaccines evaluation process that is undertaken in parallel with the regulator (Therapeutic Goods Administration) and so medicines are already identified and assessed prior to market entry. Undertaking HS for medicines and vaccines in Australia, therefore, has different implications than undertaking HS for

[5] PBS News 20 September 2023: https://www.pbs.gov.au/info/news/2023/09/international-hta-collaboration-expands

other health technologies, such as medical devices and cell and gene therapies. The latter types of technologies typically do not undergo parallel processing and so do not have any form of early warning process or HTA prior to receiving regulatory approval.

HS for any type of technology may theoretically have ancillary benefits in providing greater efficiency if both the HS and the subsequent HTA are performed by the same organisation. Opportunities for international collaboration on HS exist and may lessen the risk associated with the resource outlay required to provide a comprehensive HS system. Concentrating on potentially disruptive technologies might also be a way of reducing the scope and making the process more efficient, although criteria for determining 'potential for disruption' would have to be determined.

EVP and ESA have the potential for longer term benefits for the assessment and appraisal processes if the evidence produced following ESA is more useful for decision-making, in that it reduces uncertainty. Unfortunately, the evidence base did not provide any information on the benefits of ESA or EVP to any stakeholder. Moreover, what is undertaken as part of EVP is varied and guidance on 'best practice' does not exist.

The provision of ESA by regulatory and HTA agencies occurs in an ad-hoc manner. Usually, it is the sponsor seeking the guidance, rather than the regulatory or HTA agency proactively providing it or requiring it. Whilst ESA may theoretically benefit the medicine sponsor through better success with marketing applications and a shorter time to market access, it is unclear if the service provides good value-for-money for the agencies providing the advice.

There is a genuine opportunity for meaningful patient engagement at these early stages of technology development, where trial design and PICO aspects can be tailored to best reflect patient experience and preferences. More broadly, however, potential benefits to the health system of ESA and EVP, through being able to influence the development of evidence that address key health priorities (for example) for medicines, remain hypothetical. A small market like Australia is unlikely to have much sway with industry when trials are developed in larger markets (and with different priorities). ESA might be better targeted to the triallists themselves, perhaps through discussions with organisations like the Australian Clinical Trials Alliance, and address both Australian trials and where Australia is a site in multi-centre international trials.

Whilst it is too early to conclude if EVA, as implemented by NICE, is an effective way to address health system priorities and enable earlier access to effective technologies, coverage with evidence development in some form is likely to be beneficial if applied to high priority disease areas where there is high unmet clinical need, where a technology shows promise but there is limited evidence available demonstrating that, and where the magnitude of clinical benefit and cost-effectiveness are uncertain. A clear definition of high unmet clinical need and a prioritisation process that targets medicines in high priority disease areas would be crucial to the success of any such program. Additionally, there should be clear expectations around the development of evidence to confirm (or not) the promise of the medicine, with a range of stakeholders involved to advise and collaborate with industry on how data should be collected and interpreted. There should also

be consequences if expectations around evidence development or potential benefit are not met. See Paper 4 for further detail.

Horizon scanning and early assessment may have a role to play in preparing the evidence and the health system for new medicines, vaccines and highly specialised technologies. However, the precise purpose, timing and scope of these activities would need to be carefully thought through, along with the likely potential for creating efficiencies in the HTA process.

LITERATURE SEARCH RESULTS

The process of selecting relevant documents from grey literature (reports, guidelines and webpages of HTA agencies and governments) and peer-reviewed journal articles for this scoping review is given in the PRISMA-ScR flowchart (Figure 35).

Searches identified 57 relevant peer-reviewed articles and 30 English language documents for inclusion in this scoping review.

The documentation for many non-English speaking countries was not available in English, therefore, where possible, information was extracted from peer-reviewed journal articles.

DEFINING HTA ACTIVITIES COVERED BY THIS PAPER

This assessment contains information about HTA activities that occur at various stages in the technology lifecycle, generally earlier than traditional HTA (such as occurs to inform the PBAC). These activities have been divided into two main categories:

- horizon scanning
- early assessment

Three types of early assessment are considered:

  - early value proposition (also known as early HTA)
  - early scientific advice
  - early value assessment as an example of a coverage with evidence development activity.

Figure 15 shows the timeline of these assessments with regard to the development of the product, the accompanying research and the uncertainty related to decision-making around the product.

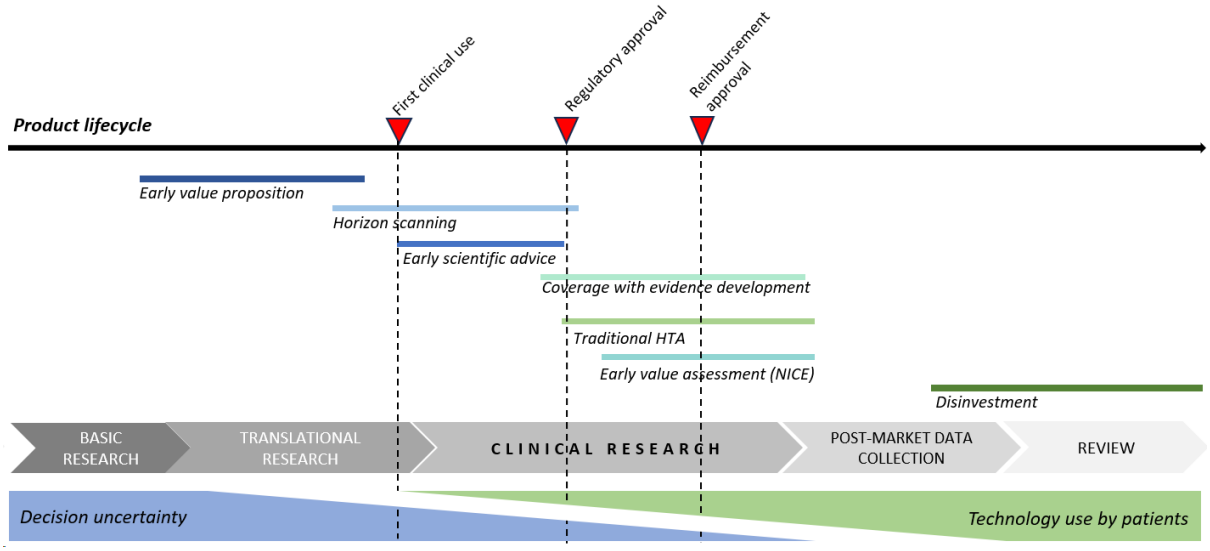

Figure 15 Types and timing of assessment and research in the technology lifecycle

Source: This figure was constructed using input from [217-219]

Note: Traditional HTA can encompass parallel processing i.e., the HTA process can start prior to regulatory approval but still uses similar methods to those usually employed after regulatory approval

Horizon scanning is an activity which aims to identify new and emerging technologies that have the potential to impact on the provision of healthcare and occurs usually between one and three years before the technology will be available. Early value proposition, often misnamed as early HTA, consists of mainly economic analyses and occurs much earlier in the product lifecycle. It is intended to guide the development of the product for the company. Early scientific advice occurs before the pivotal clinical trial, so at a time when the technology is well developed. Assessment for coverage with evidence development occurs just before, or at the same time, as traditional HTA. It should be noted that this timeline is not fixed, and activities may occur at different stages of the technology lifecycle. Each of these activities is explained more fully in the following sections. For this review, the definitions of each activity were broadly interpreted in the literature search to try to capture all relevant information, and a comparison of what is included in each type of assessment in different jurisdictions is described below.

HORIZON SCANNING

Horizon scanning is defined in the HTA Glossary as *"The systematic identification of health technologies that are new, emerging or becoming obsolete and that have the potential to effect health, health services and/or society"*, and is also listed as early awareness and alert system, which has the definition: *"A system that aims to identify, filter and prioritise new and emerging health technologies, or new uses of existing interventions; to assess or predict their impact on health, health services and/or society; and to disseminate information"*.[1]

The Glossary also includes a synonym for this, which is early warning system, defined as *"A stable unit with reliable connections and sources which aims to: identify new technologies that have the potential to make a large impact on health services; filter and prioritise these technologies to select those most likely to have an impact on health, services and budgets; and assess that impact"*.[1]

Horizon scanning is a special branch of HTA that is designed to help health systems prepare for technologies that will be impactful in some way. According to the EuroScan (now i-HTS) toolkit [219], it occurs before (or just after) market access/regulatory approval in the technology life cycle; see Figure .

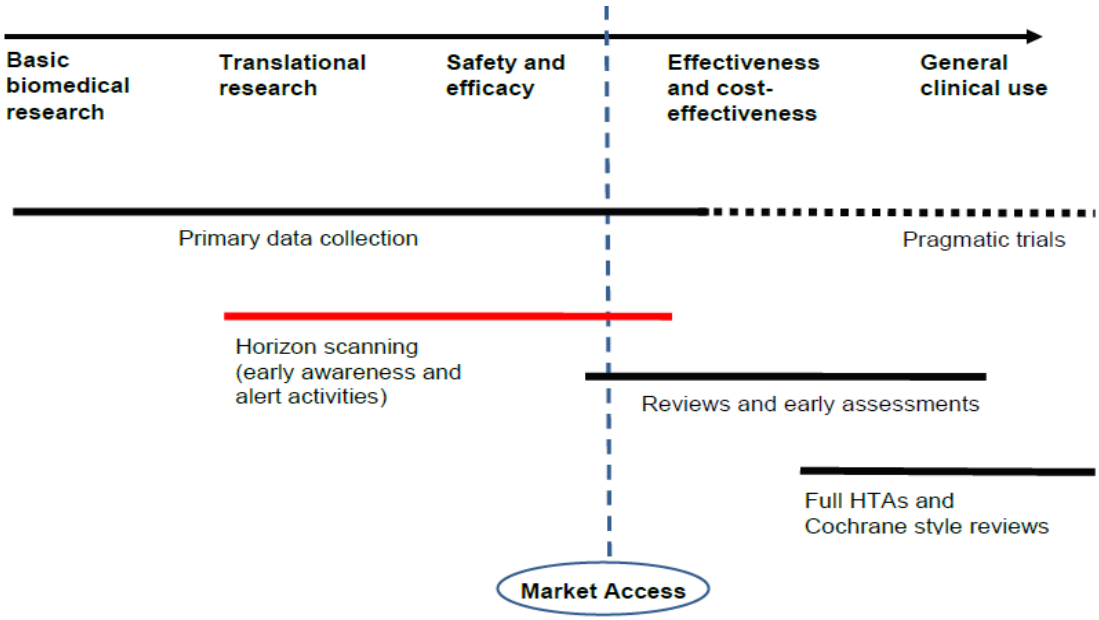

Figure 16 The continuum of HTA activities

Abbreviations: HTA = health technology assessment

Source: Reproduced from EuroScan methods tool kit 2014 [219]. This work is licensed under the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0). To view license conditions, see: http://creativecommons.org/licenses/by-nc-sa/4.0/

HORIZON SCANNING IN AUSTRALIA

Australia currently does not perform any HS activities in healthcare at the national level, although it has performed HS in the past. A timeline of both national and state HS activities in Australia is provided in Table 10. The Australia and New Zealand Horizon Scanning Network (ANZHSN) was the primary national HS body in Australia. ANZHSN was established in 2003 and was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), which had representation from each of the Australian States and Territories, the New Zealand District Health Boards, the TGA, and the Australian Government Department of Health and Ageing, and reported to the Australian Health Ministers' Advisory Council (AHMAC).[220] The States and Territory representation eventually came from local technology appraisal committees, such as VPACT, SAPACT, WAPACT, QPACT, and so the HS outcomes were disseminated through to local

technology decision-making. The ANZHSN performed HS for technologies (devices, diagnostics, procedures, or health programs), but not medicines, vaccines or blood products.

The role of the ANZHSN was to provide advance notice to policy makers of new and emerging technologies that may have positive or negative consequences on the Australian and NZ health systems. HS activities were conducted by the National Horizon Scanning Unit (NHSU) based in Adelaide and performed by two South Australian HTA agencies - the Australian Safety and Efficacy Registry of New and Interventional Procedures – Surgical (ASERNIP-S) and Adelaide Health Technology Assessment (AHTA) – the latter of which also hosted the National Horizon Scanning Unit for eight years.[220] ANZHSN was one of a small group of HS organisations that performed HS in the EuroScan collaboration and made a significant contribution. The HealthPACT secretariat was originally in the Australian Government Department of Health and then moved to the Queensland Department of Health, then the South Australian Department of Health, before HealthPACT was disbanded and funding for national HS activities ceased in 2017. HealthPACT was replaced by the Health Technology Reference Group (HTRG) but this was, in turn, disbanded when AHMAC, its parent committee, was dismantled.

The focus of HealthPACT was the improvement of the public hospital system, largely through the reduction of hospital length of stay and admissions. Topics for consideration came from clinicians who suggested technologies for evaluation early in their development. Systematic proactive data scanning for topic identification - that is typical of HS - was performed for the first eight years of the program i.e., up until the HealthPACT secretariat moved to Queensland.

The technology appraisal committees at the jurisdictional level had both an HS and basic HTA function. VPACT was established in 2005 to enable the introduction of new and existing health technologies, and in 2006-07, the Victoria government provided $4 million to fund new public health initiatives. Later, VPACT was ceased then replaced after some years by the Victorian Health Technology Program. In 2007, WAPACT was established in Western Australia, to evaluate technologies costing more than A$1 million. SAPACT was established in 2014 and has a similar role in South Australia at the time of writing this paper. Queensland Health's QPACT could perhaps be considered the most successful state program. From 2009 QPACT has successfully overseen the New Technology Funding Evaluation Program (NTFEP) which is given an annual budget to assess, fund and conduct pilot studies with a focus on technologies that have potential for value and adoption by Queensland Health.[221]

Horizon scanning for medicines in Australia was undertaken as part of NPS MedicineWise's Quality Use of Medicines stewardship activities for several years, with a particular focus on identifying medicines that might have a significant financial impact

on the Medicare Benefits Schedule and the Pharmaceutical Benefits Scheme.[6] Topics identified and approved through the horizon scanning process were then funded for programs under the NPS MedicineWise grant. Topic selection involved a range of considerations, including stakeholder input (such as surveys of General Practitioners on areas of interest to them), gaps and variation in practice, current medicine utilisation, medicine changes on the horizon (such as changes by the TGA, PBAC or overseas authorities), and current pathology and imaging utilisation. A list of 40-50 topics was identified from which a shortlist of 10 was further investigated by the formative research team from NPS MedicineWise. A report was produced which also included estimates of budget impact to the MBS and PBS and was discussed with the Clinical Intervention Advisory Group. This group then provided advice to the NPS MedicineWise executive who reviewed and recommended the priorities for the coming year. Programs were selected and designed based on criteria around meeting the mission for quality use of medicines, consumer benefit, health practitioner participation, economic impact and demonstrable impact on professional knowledge, prescribing, or ordering of tests. The NPS MedicineWise quality use of medicines work has since transitioned to the stewardship of the Australian Commission on the Safety and Quality of Healthcare (ACSQHC). According to their website, they are currently reviewing RADAR, the NPS MedicineWise service providing evidence-based information on new medicines and tests, and changes to MBS and PBS listings. No other horizon scanning activities being undertaken by ACSQHC are described.

Table 10 Timeline of horizon scanning activities in Australia

Year	National activity [220, 222]	State activity [221]
1982	HTA established in Australia	
1999	NPS MedicineWise Quality use of Medicines program established	
2003	ANZHSN established, National Horizon Scanning Unit created, overseen by HealthPACT. Secretariat in Australian Government Department of Health. Joined EuroScan.	
2005		VPACT established
2006		VPACT receives $4 million to fund new public healthcare initiatives
2007		WAPACT established to evaluate technologies costing more than $1 million,
2009		Queensland Health established QPACT; QPACT oversees NTFEP with ongoing funding for new technologies

6 NPS MedicineWise Review of the Quality Use of Medicines Program's Delivery by the National Prescribing Service Limited (NPS MedicineWise), 2019. Available at https://www.health.gov.au/resources/publications/review-of-the-quality-use-of-medicines-programs-delivery-by-nps-medicinewise?language=en

2010		VPACT funding cut to enable new systematic approach
2011	HealthPACT secretariat moved to QLD. National Horizon Scanning Unit ceased and horizon scanning sourced from a panel of organisations.	
2012	Disinvestment strategy trialled	
2014		SAPACT established
2017	Commissioned review of ANZHSN and HealthPACT undertaken. Funding for ANZHSN ceased.	Victorian Health Technology Program established
2018	Health Technology Reference Group (HTRG) created. Secretariat moved to South Australia.	
2020	AHMAC and subcommittees disbanded, including the HTRG.	
2022	NPS MedicineWise ceased operation and functions transferred to ACSQHC	

Abbreviations: ANZHSN = Australia and New Zealand Horizon Scanning Network; ACSQHC = Australian Commission on the Safety and Quality of Healthcare; HealthPACT = the national health PACT; HTA = health technology assessment; NTFEP = New Technology Funding Evaluation Program; PACT = Policy Advisory Committee on Technology; QPACT = Queensland PACT; SAPACT South Australia PACT; VPACT = Victoria PACT; WAPACT = Western Australia PACT

The HTA reference committee wrote to the State and Territory Governments in November 2023 requesting up-to-date information on horizon scanning systems and activities undertaken in each jurisdiction. The request sought information relating to the type of HS activities, governance, how technologies were identified and prioritised, and how information from HS is used. Responses were received from six jurisdictions.

Formalised HS is only undertaken in one jurisdiction in Australia at the current time, although HS activities do occur in an ad-hoc manner across the various health systems. The lack of coordination across health sectors and jurisdictions may contribute to duplication of effort and inequity.

HORIZON SCANNING UNDERTAKEN INTERNATIONALLY

For this global review, a combination of official documentation from HTA agencies or organisations (via their websites) and studies identified in the published literature search were used to populate the tables which show the process, scope and purpose of horizon scanning. Where cells are empty, information was either not identified for those criteria, or the information was not explicit enough to be certain.

Before the individual process, scope and purpose of each HS agency is explored, it is helpful to understand the international context in which agencies collaborate, and to explore more deeply the HS systems that are the most well developed.

Countries that are collaborating in or performing horizon scanning

Author Sabine Vogler published a review of the status HS in countries in the European region in 2022.[223] This article has been included as it represents the most comprehensive evidence for this paper. Vogler surveyed the public authorities of all

countries of the Pharmaceutical Pricing and Reimbursement Information (PPRI) network in the WHO European region in 2019. In the context of increasing costs of medicines, governments have been establishing pricing and reimbursement policies to maintain (or attain) financial sustainability of public funds for health care systems. HS processes have become part of that process.

There were responses on HS activity in 2019 from 44 European PPRI members. Of the 44 countries, six reported systemic use of HS within their HTA programs for the identification of new medicines, and four countries reported having ongoing HS activities, although not in a systematic way. The other 34 countries reported that there were no HS activities within the pharmaceutical policy framework in their country. Some countries without HS activities reported being involved in a cross-country collaboration which planned to conduct HS in the future. Table 11 summarises the results.

Table 11 The status of horizon scanning in European countries

Systemic HS activities		Some HS activities		No HS activities	
Collaboration (organisation)	No collaboration	Collaboration (organisation)	No collaboration	Collaboration (organisation)	No collaboration
Iceland (NPF) Italy (VD) Netherlands (IHSI) Norway (IHSI; NPF) Sweden (IHSI; NPF)	United Kingdom[b]	Austria (Beneluxa) Denmark (IHSI; NPF) Ireland (IHSI)	France	Belgium[a] (IHSI) Croatia (VD) Cyprus (VD) Finland (NPF observer) Greece (VD) Luxembourg (Beneluxa) Malta (VD) Portugal (IHSI; VD) Romania (VD) Slovenia (VD) Spain (VD)[c] Switzerland (IHSI)	Albania Armenia Belarus Bulgaria Czech Republic Estonia Germany Hungary Israel Kazakhstan Kosovo Kyrgyzstan Latvia Lithuania Moldova North Macedonia Poland Russian Federation Serbia Slovakia Turkey Ukraine

Abbreviations: Beneluxa = Belgium, Netherlands, Luxemburg, and Austria collaboration; HS = horizon scanning; IHSI = International Horizon Scanning Initiative; NPF = Nordic Pharmaceutical Forum (plans to do HS); VD = Valletta Declaration (planning to do HS)

Notes: a. Belgium is planning to do HS

b. Although not mentioned by Vogler et al NIHR Innovation Observatory in England is a member of International HealthTechScan (i-HTS; previously EuroScan)

c. HS is performed in Spain using SINETIS (Topic identification and filtration system for Spain's Early Detection and Awareness methods) for the national HTA organisation RedETS (Spanish Network of Health Technology Assessment Agencies)

Source: Vogler 2022 [223]

Cross-country HS Collaborations

Collaborations between some European countries and Canada began as early as 1997, and became the EuroScan International Network in 1999, hosted by the University of Birmingham. EuroScan had a large database of HS reports on new and emerging technologies and, to become a member of EuroScan, organisations needed to contribute their reports to the database so that they could be accessed by other members. ANZHSN was a member from around 2003 until 2017 [7] and was an active contributor but only supplied HS information on non-medicine technologies. The NHSU in Australia that conducted the HS in the early years was based in Adelaide at AHTA and was later managed by the HealthPACT secretariat in Queensland, with HS undertaken by various Australian HTA agencies.[224]

EuroScan (now known as international HealthTechScan, i-HTS), while providing a forum for collaboration on HS, coordinates the delegation of HS projects to appropriate members from its current base in Germany. Topics of interest for HS are chosen at biannual member meetings. I-HTS is driven by its members, providing a network of support, and resources which include courses, and methods advice. Capacity building is another focus of i-HTS[8].

According to Vogler the International Horizon Scanning Initiative (IHSI) was the only active cross-country collaboration in HS in 2020, when the article was written.[223] IHSI, still active today, was instigated by the Beneluxa Initiative in 2019, originally a five-country collaboration (Belgium, Netherlands, Luxemburg, Austria, and Ireland), which grew when the organisation invited additional members. IHSI is an independent legal body[9], established to provide outcomes to its members, such as fair and transparent pharmaceutical prices, and mitigation of the impact of disruptive technologies.[225] IHSI produced its own HS methodology through consultation with the Belgium Health Care knowledge Centre (KCE), who recommended setting up a central HS unit to provide resources, pilot the methodology, and manage the unit going forward. A goal of the collaboration was to launch the IHSI Joint Horizon Scanning Database by 2021 via a third-party tender, according to Vogler.[223] The IHSI website outlines their mission and methods[9].

In addition to IHSI, there are two cross-country collaborations that are planning to carry out HS. The Valletta Declaration (VD) and Nordic Pharmaceutical Forum (NPF) collaborations plan to conduct HS in the future. Of 34 countries identified in the review

[7] Australia was a member of EuroScan up until HealthPACT produced its final reports in early 2018 (Source: personal communications)
[8] International HealthTechScan (i-HTS) website: https://www.i-hts.org/
[9] International Horizon Scanning Initiative website: https://ihsi-health.org/

that were not performing HS, 12 were members of cross-country collaborations, ten were VD or IHSI members, and one was a member of both VD and IHSI (Portugal). Luxembourg was a member of Beneluxa only, and Finland had observer status only in NPF. Of the 10 countries conducting HS, only France and the United Kingdom were not cross-country collaborators. The remaining eight countries were collaborating members of IHSI, VD, Beneluxa, or NPF. Three of the eight were collaborators in both IHSI and NPF (Norway, Sweden, and Denmark).

We can take from this that only a minority of countries that are collaboration members were active in HS at the time the article was written. The implication of this is that most countries in collaborations are reliant on a small number of countries that perform HS, and even more so on the few countries that have well developed systematic HS processes.

A map published by the World Health Organization (WHO) in 2020 (Figure) illustrates the activities of European cross-country collaborations.[226] Only BeneLuxa, NPF and VD are relevant to HS collaborations. The scope, objectives, activities, and outcomes of the BeneLuxa, NPF, and VD collaborations were also summarised in the WHO report (Table 12). The scope of HS activities varies between collaborations – Beneluxa focuses on new and expensive medicines, NPF focuses on hospital medicines, and VD on new and innovative medicines. However, the objectives of VD and Beneluxa are similar in that they aim to improve patient access to otherwise hard-to-access medicines, and to support joint negotiations for pricing. NPF is a more informal platform for sharing information, but have achieved collaboration, including joint procurement, for 10 items.[226]

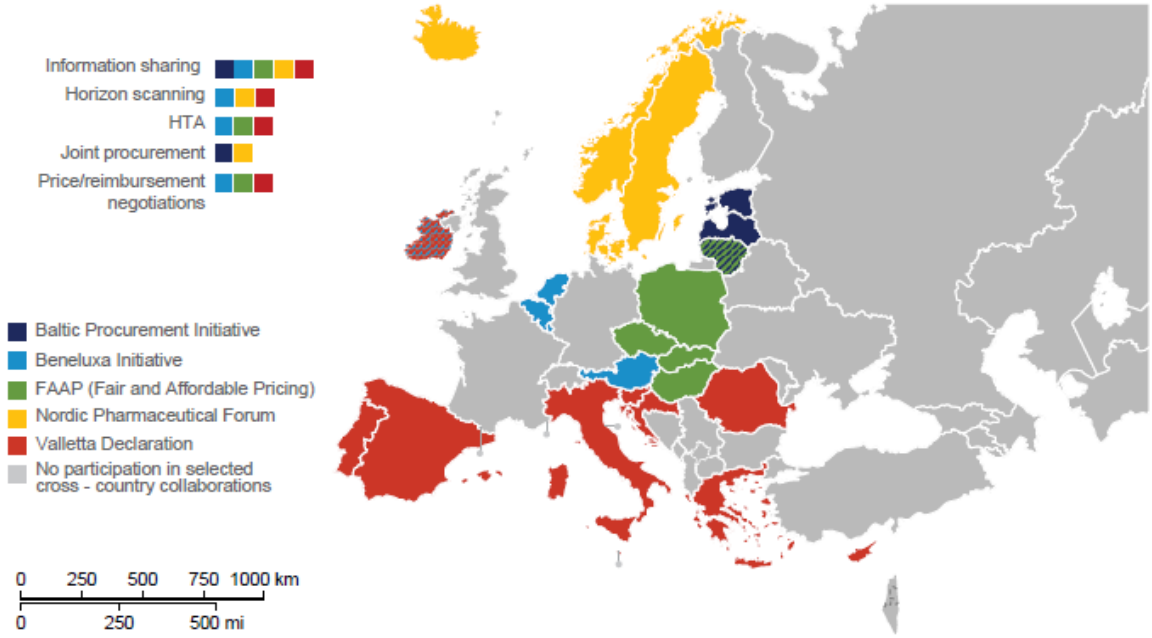

Figure 17 Activities performed by cross-country collaborations

Source: Reproduced from WHO. *Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region*. 2020 [226]. This work is licensed under the Creative Commons Attribution-NonCommercial-ShareAlike licence (CC BY-NC-SA 3.0 IGO); to view license conditions see: https://creativecommons.org/licenses/by-nc-sa/3.0/igo .

Table 12 Key characteristics of horizon scanning collaborations

Name Start date	Countries	Scope	Main objective(s)	Joint key activities	Outcomes/ developments
Beneluxa Initiative 2015	Belgium, Luxembourg, Netherlands, Austria (since 2016), Ireland (since 2018)	Mainly new and expensive medicines	• To ensure sustainable and timely access to, and appropriate use of, high-quality and affordable medicines in the participating countries	• To improve patient access to new and innovative high-cost medicines and therapies • To support the sustainability of national health systems • To achieve collaboration, leading to synergies between Member States	• International Horizon Scanning Initiative established
Nordic Pharmaceutical Forum 2015	Denmark, Iceland, Norway, Sweden, Finland (as observer)	Old and new hospital medicines	• To provide an informal platform for Nordic collaboration to identify new opportunities, benefit from information exchange and work on joint solutions with a focus on hospital medicines	•Horizon scanning • Joint procurement and negotiations • Manufacturing • Logistics • Security of supply	• Collaborative actions in all activity areas listed
Valletta Declaration 2017	Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Cyprus (since 2017), Slovenia and Croatia (since 2018)	Mainly new and innovative medicines and therapies	• To improve patient access to new and innovative high-cost medicines and therapies • To support sustainability of national health systems • To achieve collaboration, leading to synergies between Member States	• Identifying areas of cooperation, objectives and scope of work • Horizon scanning • Information sharing • HTA (joint assessment) • Joint negotiation for selected medicines	

Abbreviations: HTA = health technology assessment

Source: Modified from World Health Organization 2020 [226]

The WHO publication identified five prerequisites that were considered key elements to successful cross-country collaborations in activities such as HTA or HS.

1. Political support and commitment. Collaborations are largely politically driven so commitment to the collaboration is likely to facilitate continuity, communication with decision-makers, and involvement of high-level policy makers.
2. Resources. This is a key limiting factor in participation of collaborations. Investment in the starting phase is critical. Resources are required to establish a workforce, website set up and maintenance, for travel, to access further resources, or the commissioning of work.
3. Working structure and leadership. If these factors are of high quality they can facilitate the performance of high-quality outputs, in a time effective manner. They can also facilitate efficient use of resources, and good communication which is key in strong collaborations.
4. Organisation of health care and pharmaceutical system, including legal provisions. Countries with well organised health care structure are more likely to be able to find pathways to benefit from collaboration than those with fragmented systems. In some cases, there may be legal barriers to collaboration that would require changing to proceed.
5. Interest and willingness of industry stakeholders to engage and participate. Stake holder participation and management requires resources, but is important for successful outcomes of negotiations and collaborations.[226]

The authors propose that language, trust, and vision are further factors that require attention in collaborations. Many collaborations are established within regions where language is the same or similar, to facilitate communication. Trust and vision are characteristics of good leadership, and without them activities can falter. In addition, it was considered important to learn from previous experience in collaborations, to identify experts who are motivated and qualified to be involved, and to invest and optimise the use of information technology for communications and tools which may reduce unnecessary work hours.[226]

Countries performing integrated horizon scanning

Despite the collaborations, only six countries in the European Region are performing HS in an integrated way. The review by Vogler provided a summary of the HS processes for five of the six countries that do this. Iceland was excluded from this summary due to a lack of available data.[223] All five countries used systematic processes to identify and filter potential medicines (topics) prior to European Medicines Agency (EMA) authorisation, produced regular reports on selected topics, and used the information to help inform downstream funding decisions and assessment methods (see Figures 5, 6, 7, and 8 for flowcharts of this process). The earliest HS systems were established in the Veneto Regional Health Unit in Italy, and in the United Kingdom National Health

Service (NHS) in 2006. Others followed in 2009 (Sweden), 2013 (Norway), and 2017 (Netherlands). The aims of these current HS systems, which all assess medicines, were similar: to learn pricing to inform reimbursement decisions or negotiations; and to direct assessment pathways. Other aims were to direct planning in the regions (Italy), and to provide advance notice to health service policy bodies (UK). In Norway, HS initially provided information to support funding of medicines and other technologies for in-hospital care only, but it was extended in 2018 to outpatient care. The UK also conducts HS for all technologies, not just medicines. All five countries produce reports for government health authorities. The UK HS system produces reports for the National Health Service and for the National Institute for Health and Care Excellence (NICE), other HTA bodies and health service policy making bodies, but the UK was not a member of any cross-country collaborations in 2019.[223] The UK currently conducts HS within its National Institute for Health and Care Research (NIHR) Innovation Observatory (IO) based at Newcastle University.

It is important to note that results reported by Vogler (2022) may not include the most up to date information. However, this is largely due to a delay in the time to publishing, and so is an issue across all articles identified in the published literature search for this paper. Where more recent information was identified, it was provided. More information on European countries may be found in Table 13 to 7.

CADTH horizon scanning

CADTH is an independent, not-for-profit organisation funded by Canada's federal, provincial, and territorial governments. CADTH's role is to deliver reliable, timely, and credible evidence-based information and impartial advice to Canada's health care leaders and decision-makers through a variety of customised products and services.[227]

A comprehensive HS methodology document published by CADTH in 2017 was identified in the HTA website searches for this paper.[227] No HS publications were identified for the regional jurisdictions of Canada – Quebec, Ontario, and Alberta, which conduct other HTA activities.

According to the 2017 document, HS is the systematic identification of new and emerging health technologies (including medicines) that have the potential to impact health, health services, and/or society, and which may be subsequently considered for HTA.[227] Recent personal communication with CADTH, however, has indicated that HS is not typically conducted for medicines, but it continues for other technologies. This is because HS for medicines is not usually requested by payers, and is not undertaken proactively. However, HS for medicines still occurs occasionally as part of larger

technology reviews[10]. The processes described in the 2017 document (and below) represent methodology which is used for any technology that is considered for HS.

One of the aims for CADTH is to have maximum transparency in its HS processes. CADTH provides a timeframe for processing topics, and there is a strong focus on producing reports at different stages of the process. CADTH also actively seeks input from experts and industry. There are four phases to the HS process that focus on producing the "Issues in Emerging Health Technologies Bulletins (IEHT)". Following this process there are further publication, dissemination, and review steps.

Topic identification and prioritisation

CADTH uses a method whereby topics are identified through scanning several sources, the topics are filtered against criteria, and topics are prioritised by an HS team (Figure). Topics that are prioritised are selected for their relevance to CADTH stakeholders. Topics that are not prioritised remain in a HS database that is reviewed on a regular basis.

After management approval topics go through to the next step – research and development.

Research and development

A second flowchart illustrates the management of prioritised topics chosen for more detailed assessment (Figure). Several high-level summaries or bulletins are drafted by a Product Development team. Input is sought from various sources for these reports, including literature databases, clinical experts and industry. Bulletins are produced six to 12 times yearly, depending on available resources.

Review and approval

A third phase of HS follows in which the bulletins are reviewed, internally and externally, and a final draft is issued for approval before being published.

Publication and dissemination

In the fourth step final bulletins are published and posted on the web.

[10] Source: personal communications with Dr Lesley Dunfield, Senior Advisor, Partnerships, CADTH (August 2023)

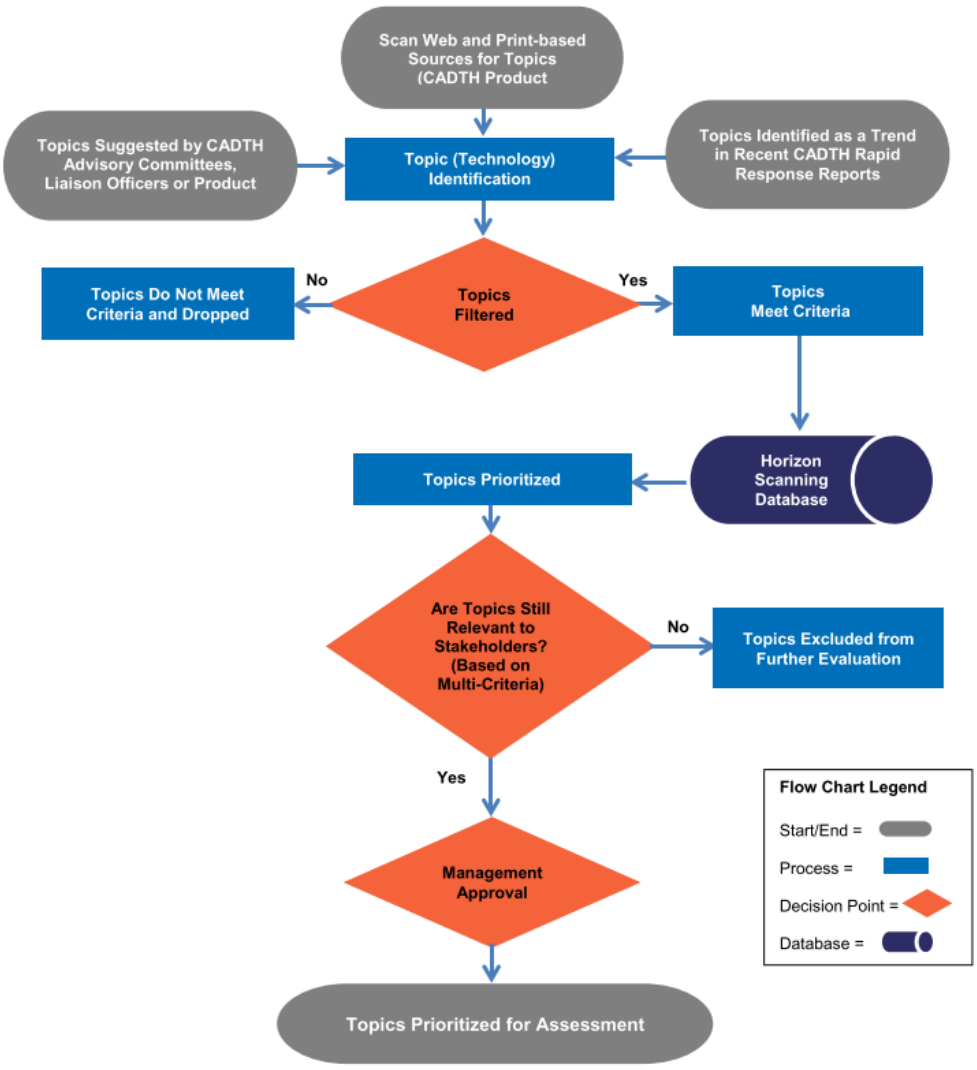

Figure 18 CADTH Topic Identification and Prioritisation Flowchart

Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health

Source: Reproduced with permission from CADTH, *Horizon scanning products and services processes*. 2017 [227]. This work is protected by the Canadian *Copyright Act.* (See https://www.cadth.ca/terms-use)

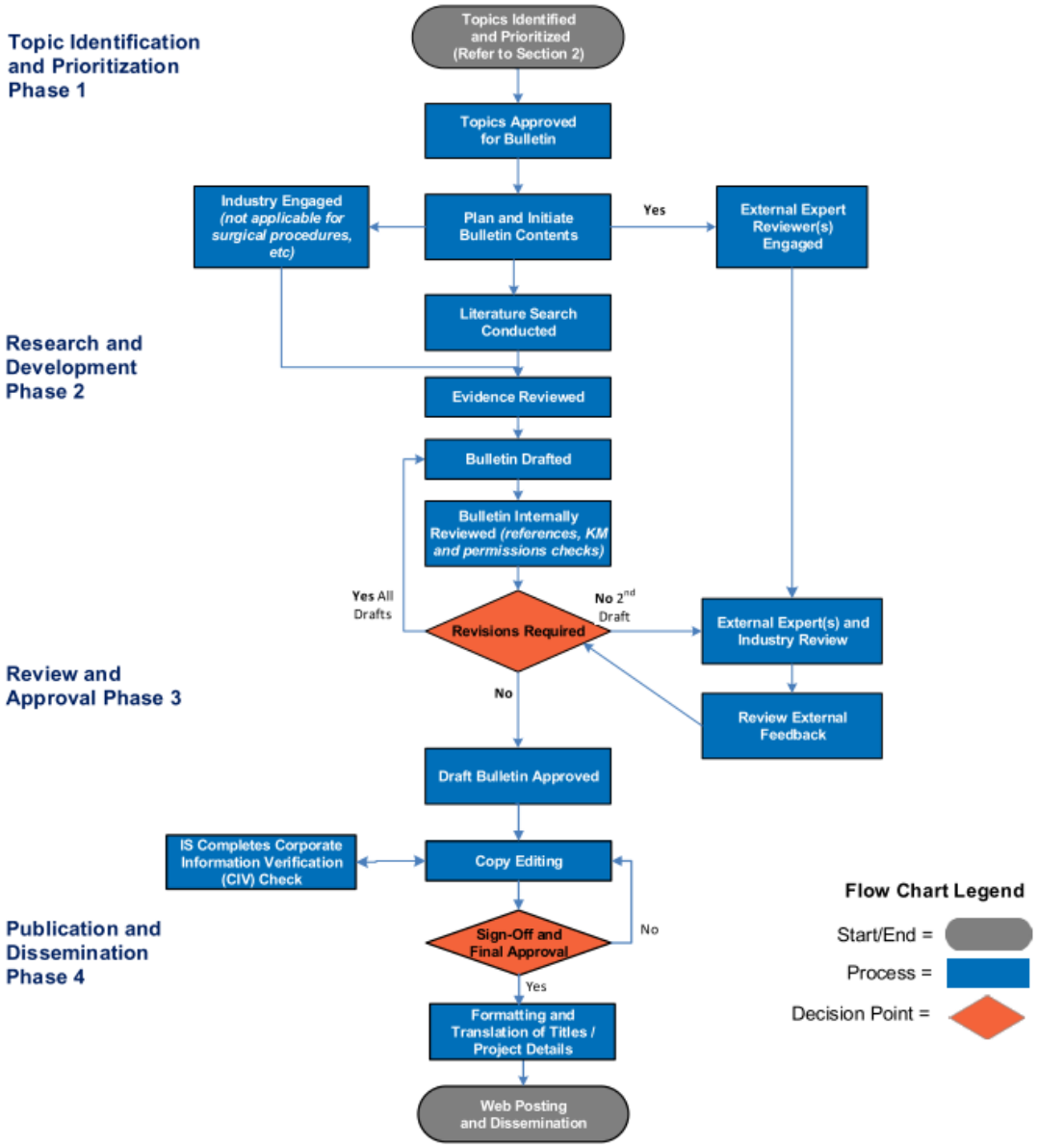

Figure 19 Issues in Emerging Health Technologies (IEHT) Bulletin Flowchart

Source: Reproduced with permission from CADTH, *Horizon scanning products and services processes*. 2017 [227]. This work is protected by the Canadian *Copyright Act.* (See https://www.cadth.ca/terms-use)

CADTH has further processes for dissemination in regularly published newsletters, and a regular compilation and publishing of new and emerging technologies.

UK horizon scanning

Horizon scanning in the UK follows a similar pathway to that performed by CADTH. Information on the methodology was not as explicit as in the CADTH guidelines, but it

is outlined in a document[27] and website[11] identified. Overall, the NICE HS system is less transparent than CADTH's process and has less emphasis on communication and dissemination of outcomes. In the UK, horizon scanning is conducted by the NIHR Innovation Observatory (NIHR-IO)[11], which also handles the dissemination aspect. According to their website, IO is "an active research centre with a focus on the provision of early awareness signals and access to timely intelligence" aimed at health care decision making on innovation. They provide an access point for industry with new medicines, acting as a gateway to NICE. This pathway provides a link between research, policy, and practice. In recent guidance, NICE indicates that evaluation timelines of topics submitted through HS activity will be based on expected regulatory approval dates and submission readiness.

The IO collates data on relevant medicines and submits them to NICE, according to criteria provided by the NICE Topic Selection Manual [27]. In their Manual, NICE lay out the pathways to assessments for various technologies, including new medicines. In a summary of the topic selection process, NICE states that it is designed to ensure that topics selected reflect the national priorities for health and care, and NICE's principles.

As an overview, topics are tested against eligibility criteria, a briefing is prepared to support decision making in selection and routing, following which the oversight panel decides on NICE's actions.

Eligibility criteria

Criteria are not listed in the manual. New medicines in their first indication or with an extension to current market authorisation are considered. Medicines that are within 24 months of regulatory approval are eligible for consideration.

Unlicensed or off-label medicines are not eligible. New generic or biosimilar medicines are not eligible for consideration if the branded version has been recommended by a NICE guideline. If there is no recommendation by NICE for the branded medicine, then generics or biosimilars can apply for selection. Prophylactic vaccinations are not eligible as they are considered by the Joint Committee on Vaccination and Immunisation (JCVI). However, therapeutic vaccinations such as some cancer treatments are considered.

Topic briefings

Briefings are developed for the topics that meet the eligibility criteria for selection. According to the NICE manual, HS briefings for medicines are developed by the IO. Briefings include:

- A description of the technology
- Intended use and position in the care pathway

[11] NICE horizon scanning program through the NIHR-IO: https://www.io.nihr.ac.uk/horizon-scanning/

- Regulatory status
- Relevant evidence
- Input from the company or person who suggested the topic
- Related NICE guidance and guidelines.

Input from the regulator, the reviewing committee, relevant experts, and relevant organisations may also be sought.

Selection and routing considerations

Eligible topics are assessed for selection against further criteria. If there is not enough information available to meet the criteria, the topic is not considered any further. For medicines, topics meeting the criteria are selected unless there is a clear rationale not to. Reasons for not selecting a medicine are listed as:

- changes to the dose, formulation or administration will not significantly affect the clinical and cost effectiveness of the medicine,
- appropriate access to the medicine is provided by an existing policy, or when a new policy can be developed (for example, not enough people are eligible to have the technology and NICE guidance would not provide value for the NHS),
- it is appropriate to assess the medicine within a NICE guideline (for example, a new medicine within an existing class).

Once selected, medicine topics are routed for technology appraisal guidance. Alternatively, medicines may meet the criteria for routing to receive highly specialised technologies guidance. The Highly Specialised Technologies Programme evaluates technologies for diseases that have the following characteristics:

- It is very rare (lower than 1 in 50,000 in England), or
- It affects a small number of the population (no more than 300 people eligible for a technology in its licenced indication and no more than 500 across all indications),
- It is a rare and severe disease that significantly shortens life or severely impairs quality of life,
- There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.

The Topic Selection and Oversight Panel

The Panel has the responsibility of the decisions made on selection and routing of HS topics that make it to selection. For medicines, the Panel decides on their selection and routing to technology appraisal or highly specialised technologies guidance. The Panel also decides whether there are inequalities to consider. This consideration is guided by

NICE's equality scheme[12]. Potential issues are included with the final scope and guidance on a topic in an equality impact assessment. Environmental sustainability is another issue assessed by the Panel.

NICE communicates the selection and routing decisions to the company involved in the submission to NIHR-IO (if a company has been the source of the topic). Topics can be reconsidered if new information is brought to the Oversight Panel's attention. In exceptional cases, NICE provides an opportunity to challenge a decision made by the Oversight Panel, or in other cases new information may require that a topic is rerouted.

US horizon scanning

HS has been conducted in the public health context in the US since 2010, operated by the Economic Cycle Research Institute (ECRI), who created the national Healthcare Horizon Scanning System for the US Agency for Healthcare Research and Quality (AHRQ).[228] The goals identified by AHRQ were:

> *"1. Create and use transparent and clearly defined processes to identify and monitor novel interventions or new uses of existing interventions in health care that might address an unmet need.*
>
> *2. Develop and implement a transparent and clearly defined framework for identifying which interventions could have the highest potential impact on clinical care, the health care system, patient outcomes, and costs.*
>
> *3. Evaluate components of existing horizon scanning systems and their respective protocols to identify best practices and effective methods of horizon scanning."*[228]

Based on these concepts, the Patient Centered Outcomes Research Institute (PCORI) took over the scanning process, but in 2018 changed the scope to *"focus on interventions with high potential for disruption in the United States in 5 focus areas: Alzheimer's disease and other dementias; cancer; cardiovascular diseases; mental and behavioural health conditions; and rare diseases."* Since then, there has been additional expansion in HS to include COVID-19 interventions.[228]

Further expansion occurred in 2020, when ECRI/PCORI began the establishment of a database and website for HS activities. The database, built on *"a secure, cloud-based platform"*, is freely available to all stakeholders through its website and it went live in 2021.[13] An overview of the PCORI HS process can be seen in Figure 20.

[12] NICE equality scheme: https://www.nice.org.uk/about/who-we-are/policies-and-procedures/nice-equality-scheme

[13] PCORI Horizon Scanning Database: https://horizonscandb.pcori.org/

While ECRI is a not-for-profit government organisation, PCORI HS activities are only partially publicly funded. PCORI funds were initially established through the US government *Patient Protection and Affordable Care Act* of 2010, but later, income from Treasury and a fee assessed on private insurance and self-insured health plans (the PCORI Trust Fund Fee) were incorporated.[228]

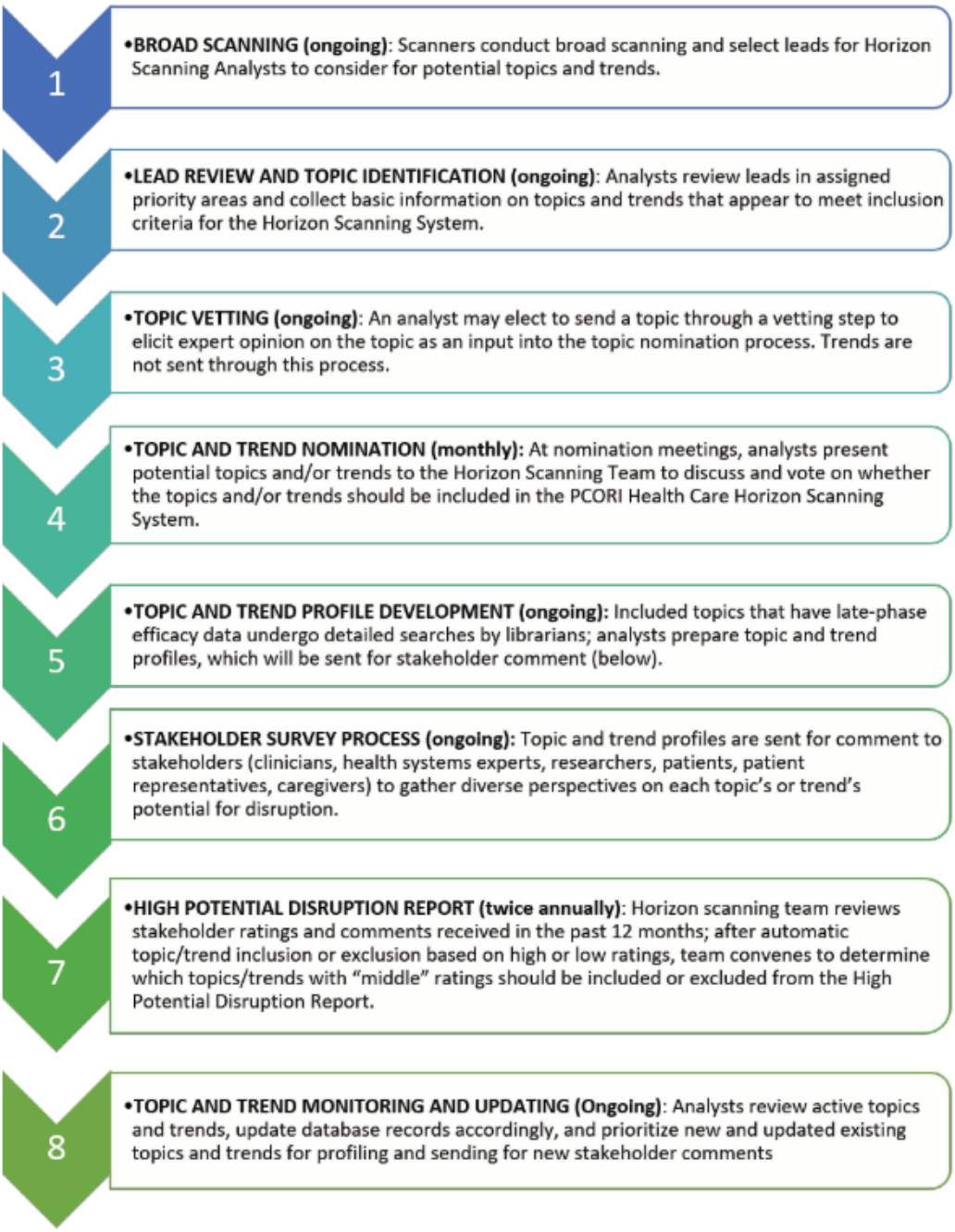

Figure 20 PCORI Health Care Horizon Scanning System Process Overview

Source: Hulshizer et al 2022 [228] Reproduced under ©2011-2023 Patient-Centered Outcomes Research Institute Terms of Use which allows use without special permission for Public Domain documents.

SUMMARY OF KEY POINTS FOR PROCESS, GOVERNANCE, SCOPE AND PURPOSE OF HORIZON SCANNING PROGRAMS

There was limited evidence available for extraction into the tables, but they were populated using the most recent information located on HTA websites or in the literature, identified through the searches described in Appendix 1. Cells were left empty in Tables 2 to 4 if no data were identified. Where Vogler [229] reported that there was HS conducted in a country, then this was recorded in the tables, unless a more recent publication reported on a particular jurisdiction. It was not possible to rule out specific characteristics of HS, as we could not be certain that we had identified all available data on HS within the allocated timeframe. It was also difficult to say categorically that the references used in this paper contained the latest information, however best estimates of the latest and most accurate information were used. It was also noted that HTA and HS websites were frequently not up to date, accurate or detailed. For example, recent communications (August and December 2023) with CADTH indicated that medicines are not typically considered in their formal HS program, but this wasn't reflected on the website. NICE, CADTH, and ECRI/PCORI (overseen by AHRQ) were nevertheless identified as the primary HS organisations world-wide, with established HS programs, so a special focus on the processes that are used in those organisations was included.

Horizon scanning process and governance

With respect to horizon scanning, the following were considered:

- Is horizon scanning proactive (selecting topics and scanning technologies without submissions), reactive (topic is selected through submissions), or a combination?
- Who decides what technology is scanned?
    - Government
    - Private healthcare
    - Industry
    - Consumers / clinicians / submission based.
    - Combination
- How are horizon scanning systems funded? (Government or non-Government?)
- In addition to Government / payers, are stakeholders involved in horizon scanning?
    - Consumers
    - Clinicians
    - Industry
    - Other
- Who performs the horizon scanning?
    - Government
    - Academia

- Clinicians
- Industry
- Other

Table 13 provides a summary of the information extracted from the literature and websites on these elements.

Table 13 Process and governance of horizon scanning

Jurisdiction (Collaboration member)		1 Proactive vs Reactive	2 Who suggests/submits potential technologies for horizon scanning?				3 Funded by	4 Stakeholders involved				5 Who performs the horizon scanning?
Categories		Proactive, Reactive, Mixed	Government	Private healthcare	Industry	Consumers	Government (Govt), Industry, other.	Consumers	Clinicians	Industry	Other	Pick one of: Government Academia Clinicians Industry Other
Australia	No current program for HS	●	●	●	●	●	●	●	●	●	●	●
Austria [229] (EuroScan; Beneluxa)	AIHTA[a], HSO	◑ (limited activities)	●	○	○	○	Govt	○	○	○	○	Government
Belgium [223] (IHSI; Beneluxa)	No HS system in 2019 (plans to start HS)	●	●	●	●	●	●	●	●	●	●	Agreement for HS collaboration
Brazil [230]	CONITEC[a]	● Reactive	●	○	○	○	Govt	○	○	○	○	Government
Canada [227]	CADTH[a] (national HTA agency)	● Combined	●	●	●	● All stake-holders	Govt	●	●	●	Ministries of Health, hospitals and health institut'ns, health regions, care-givers	Government
Denmark [231] [223] (IHSI; NPF)	DACEHTA	◑ (limited activities)	○	○	○	○	Govt	●	●	●	○	Government

Jurisdiction (Collaboration member)		1 Proactive vs Reactive	2 Who suggests/submits potential technologies for horizon scanning?				3 Funded by	4 Stakeholders involved				5 Who performs the horizon scanning?
Categories		Proactive, Reactive, Mixed	Government	Private healthcare	Industry	Consumers	Government (Govt), Industry, other.	Consumers	Clinicians	Industry	Other	Pick one of: Government Academia Clinicians Industry Other
Finland [223] (NPF observer)	No HS system in 2019 (may plan to start HS)	●	●	●	●	●	●	●	●	●	●	Agreement for HS collaboration
France [223]	Haute Authorité de Santé[a] (HAS)	◑ (limited activities)	○	○	○	○	○	○	○	○	○	Unknown (HS performed by several organisations)
Germany [223]	No HS system in 2019	●	●	●	●	●	●	●	●	●	●	●
Iceland [223] (IHSI; NPF)	IMA	● Proactive (systematic use in develop-ment)	○	○	○	○	○	○	○	○	○	○
Ireland [232 223] (IHSI)	HPRA	● Proactive	○	○	○	○	Govt	○	○	○	○	Government
Israel [223]	No HS system in 2019	●	●	●	●	●	●	●	●	●	●	
Italy [233 223] (VD)	AIFA HSS	● Proactive	●	○	○	○	Govt	○	○	○	○	○
Malaysia [234 235] AIHTA	MaHTAS	● Proactive	●	○	○	○	Govt	○	○	○	○	Government
Norway [223, 236] (IHSI; NPF)	NIPH[a] NMA	● Proactive	●	●	●	● Any	Govt	●	●	●	○	Government & industry

Jurisdiction (Collaboration member)		1 Proactive vs Reactive	2 Who suggests/submits potential technologies for horizon scanning?				3 Funded by	4 Stakeholders involved				5 Who performs the horizon scanning?
Categories		Proactive, Reactive, Mixed	Government	Private healthcare	Industry	Consumers	Government (Govt), Industry, other.	Consumers	Clinicians	Industry	Other	Pick one of: Government Academia Clinicians Industry Other
						stake-holder						
Poland [223]	No HS system in 2019	●	●	●	●	●	●	●	●	●	●	●
Singapore [237]	ACE[a]	● Combined	●	●	●	○	Govt	○	●	○	Medical Technology Advisory Committee; policy makers	Government
Spain [223, 238b] (VD)	RedETS/ SINETSIS	● Proactive	○	○	○	◑ Secondary sources: experts, literature	○	○	○	○	○	○
Sweden [223, 239] (IHSI; NPF)	Swedish EAA System (medicines only)	● Proactive	○	●	○	○	Govt	○	●	●	○	Working groups of pharmacists
Switzerland [223] (IHSI)	No HS system in 2019	●	●	●	●	●	●	●	●	●	●	Agreement for collaboration
The Netherlands [223] (IHSI)	DHI/ Horizonscan+	● Proactive	○	○	○	○	○	○	○	○	○	○
United Kingdom [223]	Wales, AWTTC [240]	● Combined	●	○	●	○	Govt	○	●	●	○	Government & industry

Jurisdiction (Collaboration member)		1 Proactive vs Reactive	2 Who suggests/submits potential technologies for horizon scanning?				3 Funded by	4 Stakeholders involved				5 Who performs the horizon scanning?
Categories		Proactive, Reactive, Mixed	Government	Private healthcare	Industry	Consumers	Government (Govt), Industry, other.	Consumers	Clinicians	Industry	Other	Pick one of: Government Academia Clinicians Industry Other
	Scotland, SMC [241]	● Combined	●	○	●	○	Govt	○	●	●	○	Government
	NICE[a]/NIHR[a]-IO[27] [242]	● Combined	●	●	●	● Members of the public	Govt	○	○	○	○	Government (NIHR-IO)
USA [228]	ECRI/PCORI	● Proactive	○	○	○	○	Mixed	●	●	●	●	Contracted to independent body

Abbreviations: AIFA HSS = Italian Medicines Agency Horizon Scanning System; AWTTC = All Wales Therapeutics and Toxicology Centre; DACEHTA = Danish Centre for Evaluation and Health Technology Assessment; DHI = Dutch Health Institute; EAA system = early awareness and alert system; ECRI = Economic Cycle Research Institute; HPRA = Health Products Regulatory Authority; HTA = health technology assessment; HS = horizon scanning; IHSI = International horizon scanning Initiative; IMA = Icelandic Medicines Agency; IO = Innovation Observatory; MaHTAS = Malaysian Health Technology Assessment Section; NMA = Norwegian Medicines Agency; NPF = Nordic Pharmaceutical Forum; OECD = Organisation for Economic Co-operation and Development; PCORI = Patient-Centered Outcomes Research Institute; RedETS = Spanish Network of Health Technology Assessment Agencies; SINETIS = Topic identification and filtration system for Spain's Early Detection and Awareness methods; SMC = Scottish Medicines Consortium; VD = Valletta Declaration

Notes: a. Refer to Appendix 2, for names of INAHTA Agencies

b. While Vogler reported that there were no HS activities in Spain, an abstract of an oral presentation from 2022 indicated that SINTESIS has been operating for a few years and feeding information to the Spanish Network of Health Technologies Assessment Agencies (RedETS) [238].

● Yes ◑ Partial ● No ○ Not reported/No information found

Is horizon scanning proactive?

Proactive HS is conducted mostly in the European region. The United Kingdom (including Wales and Scotland jurisdictions), The Netherlands, Taiwan, Sweden, Spain, Singapore, Norway, Malaysia, Italy, Ireland, the USA, and Canada (12 countries) are performing proactive or systematic HS to inform their healthcare services[14]. Along with USA and Canada, Spain uses a specialised tool or system for proactive topic selection and prioritisation.[15] Although it was not always explicit in the data, countries conducting proactive or systematic HS are also likely to be conducting reactive HS. Four countries – Austria, Brazil, Denmark, and France – are conducting reactive or limited HS activities only. Iceland was noted to be in the process of establishing systematic HS processes. From the data collected, Brazil, Canada, Malaysia, Singapore, UK, and USA are the only countries conducting HS outside of Europe. Although active HTA agencies were identified for Japan, Taiwan, South Korea, and Uruguay, a current HS system could not be confirmed in these countries. South Korea has a separate pathway for the assessment of innovative technologies, but an early scanning step is not explicitly conducted[16].

Who decides what technology is scanned?

Twelve jurisdictions reported on how topics were suggested for HS consideration. In 10 jurisdictions (including 3 within the UK) governments contributed to topics, in five jurisdictions private healthcare providers could contribute, in six jurisdictions industry could contribute, and in three jurisdictions consumers could contribute to topics for consideration. The latter three jurisdictions - the United Kingdom, Canada, and Norway - all have well established HS organisations (NICE, CADTH, and NIPHNO respectively) that enable input from consumers and clinicians. In Norway any stakeholder "can and is expected to provide input" according to Vogler.[223] According to NICE HS methods anyone, "including health and care staff and members of the public" can make topic suggestions by emailing the topic selection team at NICE [27]. Similarly, in the CADTH methodology guidelines patients and clinicians are listed amongst those that can suggest topics by emailing the HS team.[227] It should be noted that CADTH no longer includes medicines as topics for consideration in HS.[7]

How is horizon scanning funded?

All jurisdictions that reported the funding source for HS (15 in all), used government funding (taxation or social insurance), either directly or through various government

[14] Until recently, medicines were included in the HS program at CADTH, however, according to personal communications, formal HS is now only carried out for devices and diagnostic technologies. HS for medicines is occasionally performed as part of larger technology reviews.
[15] The Spanish priority scoring tool PriTec: https://www.ipaac.eu/roadmap/detail/65
[16] Innovative HTA, Korea: https://nhta.neca.re.kr/nhta/eng/nhtaENG0101VA.ecg

agencies [243]. Vogler (2022) reviewed government initiatives in HS so industry or other funded schemes were not identified through this article.[223]

In the USA, the Economic Cycle Research Institute (ECRI) performs horizon scanning, initially under contract with the Agency for healthcare and Research Quality (AHRQ), but now for the Patient-Centred Outcomes Research Institute (PCORI).[228] PCORI funds were established through the US government *Patient Protection and Affordable Care Act* of 2010, but under a 2019 amendment now receives income from statutory appropriations from the general fund of the Treasury and a fee assessed on private insurance and self-insured health plans (the PCORI Trust Fund Fee)[17]

In addition to Government / payers, are stakeholders involved in horizon scanning?

Information from 10 jurisdictions (including the United Kingdom and Wales) indicated which stakeholders are providing input into HS decision making. HS organisations in Canada (CADTH)[14], Denmark, Norway, United Kingdom (NICE), the USA, and Wales indicate they engage with clinicians, consumers, and industry in their processes. In Wales, industry meets with representatives of the All Wales Therapeutics and Toxicology Centre (AWTTC) to provide two way communication.[240] The AWTTC is the HS team within the HTA organisation All Wales Medicines Strategy Group (AWMSG), which claims to have representative members from a broad range of stakeholders, and also engages with clinical experts, financial and clinical service providers and patient interest groups. NICE engages with a similar large range of stakeholders [27]. Swedish HS engages with clinical pharmacologists and clinicians.[239]

Who performs the horizon scanning?

Data indicated that government agencies performed the HS in all jurisdictions. When described, HS was usually performed by government or industry appointed experts. One exception was the Swedish Early Awareness Alert (EAA) system. Swedish EAA assigns small teams of pharmacists to each potential new medicine who then engage with relevant experts such as clinical pharmacologists and clinicians. The teams are responsible for early identification, filtration, prioritisation, early assessment, and dissemination of results.[239] In the USA, ECRI is contracted to do HS. ECRI is an independent non-profit organisation.[228]

[17] How PCORI is funded: https://www.pcori.org/about/about-pcori/financials-and-reports/our-fundingbn

Scope of horizon scanning

With respect to the scope of horizon scanning for medicines, the following were considered:

- What type of technologies are targeted (alternative term: prioritised) via horizon scanning?
    - High cost
    - Highly effective (large efficiency or health gains)
    - Disruptive (requiring changes to facets of the health care system)
    - High unmet need
    - Rare disease or special populations
    - Other
- What is the time horizon considered for horizon scanning?

Data were extracted on each of these scope elements in Table 14.

From the literature it was noted that most HS organisations used a sequence of topic identification (usually through scanning multiple sources), filtration using specified criteria, and prioritisation which could lead to assessment, reporting and dissemination. An example of workflow for HS from the Agency for Care Effectiveness (ACE) in Singapore is given in Figure 21, and from the NIHR-IO (NICE) in Figure 22.

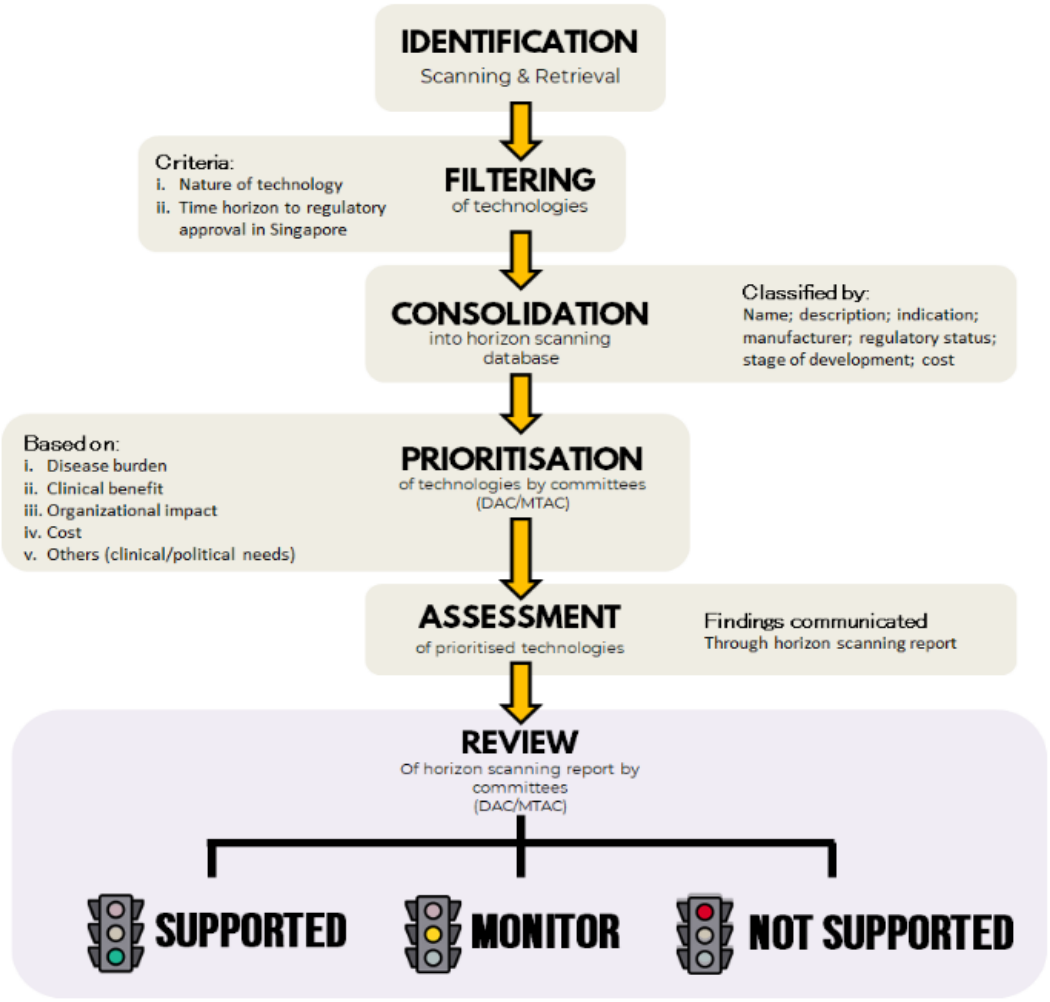

Figure 21 Overview of ACE's horizon scanning system

Source: Reproduced with permission from ACE, *Horizon Scanning Methods and Process Guide,* Ministry of Health, Singapore 2021.[237]. This work is protected under copyright: © Agency for Care Effectiveness, Ministry of Health, Republic of Singapore All rights reserved.

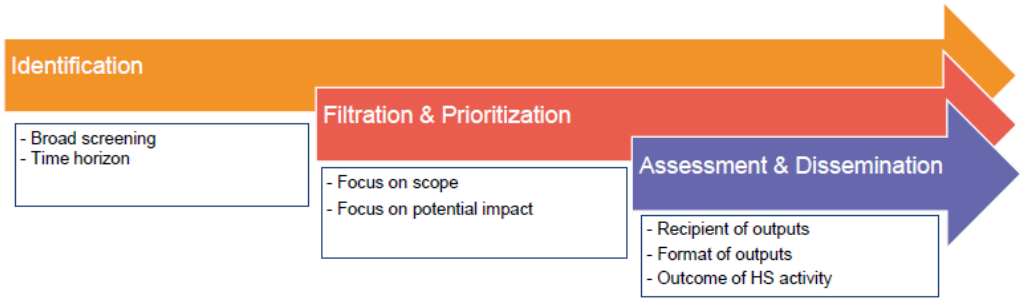

Figure 22 Overview of the NIHR-IO horizon scanning system

Source: Reproduced with permission from NIHR, *Horizon scanning of innovative medicines, devices, diagnostics, and digital technologies for stakeholders in England*, workshop presentation. 2021.[242] This work is protected under copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne

Table 14 Scope of horizon scanning

Jurisdiction (collaboration member)		1 Type of technology						2 Time horizon
		High Cost	Highly Effective	Disruptive/ organisational implications?	Unmet need	Rare disease	Other	3yr, 5yr, 10yr, Other
Australia	No current program for HS	●	●	●	●	●	●	●
Austria [229, 244] (BeneLuxa)	AIHTA[a]-HSO	●	●	●	●	●	Oncology and COVID19 medicines, vaccines	○
Belgium [223] (IHSI; Beneluxa)	No HS system in 2019 (plans to introduce HS)	●	●	●	●	●	●	●
Brazil [230]	CONITEC[a]	●	●	○	○	●	Medicines with impact that may result in future judicial action	○
Canada [227]	CADTH[a] (national HTA agency)	●	●	○	●	●	New or innovative, impact on health disparities	○
Denmark [223, 231] (IHSI; NPF)	DACEHTA (limited HS activities)	○	○	○	○	○	○	○
Finland [229] (NPF observer)	No HS in 2019	●	●	●	●	●	●	●
France [223]	HAS[a] (limited HS activities)	○	○	○	○	○	○	○
Germany [223]	No HS in 2019	●	●	●	●	●	●	●
Iceland [223] (IHSI; NPF)	IMA	○	○	○	○	○	○	○
Ireland [223, 232] (IHSI)	HPRA	○	○	○	○	○	○	○
Israel [223]	No HS in 2019	●	●	●	●	●	●	●

Jurisdiction (collaboration member)		1 Type of technology						2 Time horizon
		High Cost	Highly Effective	Disruptive/ organisational implications?	Unmet need	Rare disease	Other	3yr, 5yr, 10yr, Other
Italy [233] [223] (VD)	AIFA HSS	●	●	●	●	●	Availability of double-blind RCT evidence	Typically 2-3 years before MA
Malaysia [234]	MaHTAS	●	○	○	●	○	Local innovations	Within 24 months of MA
Norway [223, 236] (IHSI; NPF)	NIPH[a] NMA	●	●	○	○	○	Innovation, use in specialist health service	As early as possible before MA
Poland [223]	No HS system in 2019	●	●	●	●	●	●	●
Singapore [237]	ACE	●	●	●	●	○	political needs can be a consideration (limited activities for medicines and cell and gene therapies)	Varied -typically 2-3 years before MA
Spain [223, 238b] (VD)	RedETS/SINTESIS	○	○	○	○	○	○	○
Sweden [239] [223] (IHSI; NPF)	Swedish EAA System (medicines only)	●	●	●	●	●	Likely high impact and accelerated assessment by the EMA; media and patient group interest; legal, ethical or political aspect; anticipated sub-optimal market uptake; high level of innovation; new disease application	Within 1-3 years of MA
Switzerland [223] (IHSI)	No HS system in 2019	●	●	●	●	●	●	●
The Netherlands [223] (IHSI)	DHI/Horisonscan+	●	○	○	○	○	○	Within 2 years of MA
United Kingdom	Wales, AWTTC [240]	○	○	○	○	○	○	○
	Scotland, SMC[a] [241]	●	○	●	●	○	○	○

Jurisdiction (collaboration member)		1 Type of technology						2 Time horizon
		High Cost	Highly Effective	Disruptive/ organisational implications?	Unmet need	Rare disease	Other	3yr, 5yr, 10yr, Other
	NICE[a]/NIHR[a]-IO [27, 242]	●	●	○	●	●	Potential to impact equity, equality or environmental sustainability; medicines expected to get regulatory approval within 2 years	Within 3-5 years of MA
USA [228]	ECRI/PCORI	○	○	●	○	○	○	○

Abbreviations: AIFA HSS = Italian Medicines Agency Horizon Scanning System; AWTTC = All Wales Therapeutics and Toxicology Centre; DACEHTA = Danish Centre for Evaluation and Health Technology Assessment; DHI = Dutch Health Institute; EAA system = early awareness and alert system; ECRI = Economic Cycle Research Institute; HPRA = Health Products Regulatory Authority; HTA = health technology assessment; HS = horizon scanning; IHSI = International horizon scanning Initiative; IMA = Icelandic Medicines Agency; IO = Innovation Observatory; MA = market authorisation; MaHTAS = Malaysian Health Technology Assessment Section; NMA = Norwegian Medicines Agency; NPF = Nordic Pharmaceutical Forum; OECD = Organisation for Economic Co-operation and Development; PCORI = Patient-Centered Outcomes Research Institute; RedETS = Spanish Network of Health Technology Assessment Agencies; SINETIS = Topic identification and filtration system for Spain's Early Detection and Awareness methods; SMC = Scottish Medicines Consortium; VD = Valletta Declaration

Notes: a. Refer to Appendix 2 for names of INAHTA Agencies

b. While Vogler reported that there were no HS activities in Spain, an abstract of an oral presentation from 2022 indicated that SINTESIS has been operating for a few years and feeding information to the Spanish Network of Health Technologies Assessment Agencies (RedETS) [238].

● Yes ◑ Partial ● No ○ Not reported/No information found

Amongst HS organisations for which a publication about methods was identified, most used a process of topic identification through scanning, filtration, and topic prioritisation and/or selection for HS reporting. In some cases, criteria were clearly listed and in others, they were identified or implied within the text. As an illustration of HS processes, an article by Eriksson et al provided a clear outline of Swedish HS processes (Figure), along with a list of filtration criteria (Figure).[239]

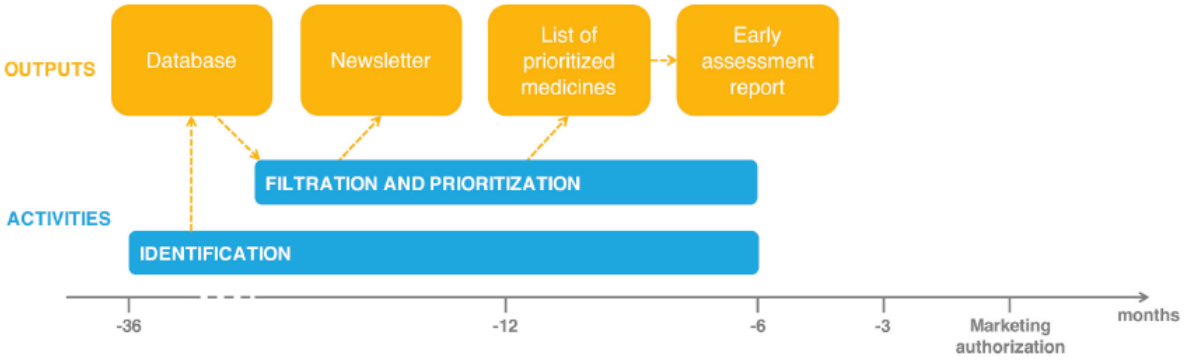

Figure 23 Activities and outputs of the Swedish EAA System

Source: Reproduced from Eriksson I. et al. *The Early Awareness and Alert System in Sweden: History and Current Status*. Front Pharmacol, 2017 [239]. This work is licensed under the Creative Commons Attribution License (CC BY 4.0). To view license conditions, see: https://creativecommons.org/licenses/by/4.0/

Box 1 | Filtration criteria.

Size of patient population
Severity of the disease
Potential to clinically improve patient outcomes
Innovative way of treating the disease
Potential to affect treatment costs
May require reorganization of the healthcare system
Potential to influence treatment guidelines
Potential safety issues
Potentially high media/public interest
Non-optimal introduction rate following marketing authorization
Potentially legally, ethically, or politically interesting

It is also taken into consideration whether the medicine/indication:
Belongs to a growing class of medicines or therapeutic area
Represents a new form of treatment or a new class of medicines
Is revelant to Swedish conditions
Is in late phase clinical trials (Phase II or Phase III) or is submitted to regulatory agencies

Figure 24 Filtration criteria of the Swedish EAA System

Source: Reproduced from Eriksson I. et al. *The Early Awareness and Alert System in Sweden: History and Current Status*. Front Pharmacol, 2017 [25]. This work is licensed under the Creative Commons Attribution License (CC BY 4.0). To view license conditions, see: https://creativecommons.org/licenses/by/4.0/

Type of technology

Twelve countries or jurisdictions reported some information on the type of technology that was considered within their HS program. Cost was the most common reason specified for considering a medicine for HS, and 10 jurisdictions reported this as a reason, although the manner of reporting varied. Criteria included were those likely to be high cost (Brazil), have significant impact on health care resources (CADTH, ACE), likely to have high treatment cost per year (Italy, Sweden), facilitate budgetary planning (Malaysia), high-cost relative to comparators (Scotland), or likely budget impact (the Netherlands, Norway).

The effectiveness of a new medicine was considered closely alongside cost and was a criterion reported by seven countries. Articles reported expected impact on clinical patient outcomes (Sweden, CADTH), potential therapeutic value (Italy), safe and effective (Norway), and clinical benefit (Singapore). However, it has been noted that CADTH no longer performs formal HS for medicines[7]. The information included in the table is the most recent identified through searches of HTA websites and the literature databases associated with this paper.

Disruptive technologies were specifically prioritised by six jurisdictions, and it was noted that consideration of likely organizational impact was an inclusion in the European EAA model of HS.[245] Countries that considered a technology if it was going to have organisational impacts were also included in this category. The Scotland HS system considered medicines and defined high impact as those that had *"a predicted net budget impact (relative to comparators) for NHS Scotland of greater than £500,000 per annum or may be associated with major service implications"*. The Swedish EAA System criteria specifies that medicines *"may require reorganisation of the healthcare system"* (Figure). The USA HS organisation, ECRI, prioritises technologies with likely disruptive potential within the next 3 years. Singapore and Italy also assess potential organisational requirement or impact of new medicines.

The NICE manual on topic selection has a pathway for highly disruptive technologies, however it is not an option for medicines. It is available to new interventional procedure topics (devices, diagnostic, digital, combination or integrated topics) [27]. The NHIR-IO website does not state that disruptive medicines are prioritised.

Eight countries prioritised technologies that were for rare diseases, or for unmet clinical need, or both. High burden of disease, size of the patient population and severity of disease were the characteristics most often stated as criteria amongst these countries when considering medicines that have the potential to make an impact. For example, Singapore HS is focused on technologies which address issues with the biggest disease burden.

Other criteria for the type of technology prioritised were mentioned by nine HS organisations. CADTH looked for medicines that are new or innovative, and likely to impact on health disparities[14]. Similarly, NICE criteria were inclusive for technologies that have the potential to impact equity and equality, but also environmental sustainability. Malaysia and Norway prioritised innovative medicines, and Malaysia

particularly focused on local innovation. Sweden included medicines that were likely to have political impact, while Singapore ACE methods provide the potential to consider political needs when prioritising technologies [237] (although the degree to which this is used for medicines may be limited). Brazil prioritised medicines that were likely to lead to future judicial action. Austria's HS system prioritises oncology and COVID-19 medicines.

Time Horizon

A time horizon was not often reported as a criterion for consideration of a new medicine for HS. NICE, Malaysia, and the Netherlands included medicines that were within 2 years of market authorisation, whereas Sweden stated new medicines met the criteria if they were 1 to 3 years away from market authorisation. The Swedish EAA reports are usually published within 6 months of market authorisation.[239] Norway noted that new medicines were considered as early as possible prior to market approval. [223]

Purpose of horizon scanning

With respect to horizon scanning, the following elements were considered:

- Purpose of horizon scanning?
    - Identify required changes to health care systems (planning service delivery)
    - Engage early with stakeholders
    - Engage early with industry
    - Identify evidence limitations that could be addressed.
    - Inform approach to assessment (regulatory / HTA)
    - Identify whether existing funding arrangements require re-consideration.
    - Other (key risks in implementation, gaps in current health care provision)

Table 15 summarises the information extracted from literature and websites that addressed these elements.

Table 15 Purpose of horizon scanning

Jurisdiction (collaboration member)		1 Purpose						
		Planning	Engage Stakeholders	Engage Industry	Identify evidence limitations	Inform approaches to assessment	Review existing funding arrangements	Other
Australia	No current program for HS	●	●	●	●	●	●	●
Austria [229, 244] (BeneLuxa)	AIHTA[a], HSO	●	○	○	○	○	○	○
Belgium [223, 229] (IHSI; BeneLuxa)	No HS system in 2019 (plans to introduce HS)	●	●	●	●	●	●	●
Brazil [230]	CONITEC[a]	●	○	○	○	○	○	To support the defence of the decisions of the MoH in court; to support the development of clinical guidelines
Canada [227]	CADTH (national HTA agency)	●	●	●	●	●	○	review feedback, publication and dissemination of bulletins & newsletters
Denmark [231 223] (IHSI; NPF)	DACEHTA	●	○	○	○	●	○	○
Finland [223] (NPF observer)	No HS system in 2019	●	●	●	●	●	●	●
France [223]	HAS	○	○	○	○	○	○	○

Jurisdiction (collaboration member)		1 Purpose						
		Planning	Engage Stakeholders	Engage Industry	Identify evidence limitations	Inform approaches to assessment	Review existing funding arrangements	Other
Germany [223]	No HS system in 2019	●	●	●	●	●	●	●
Iceland [223] (IHSI; NPF)	IMA	○	○	○	○	○	○	○
Ireland [232 223] (IHSI)	HPRA	●	○	○	○	○	○	Research and innovation
Israel [223]	No HS system in 2019	●	●	●	●	●	●	●
Italy [223, 233] (VD)	AIFA HSS	●	○	●	○	○	○	○
Malaysia [234]	MaHTAS	●	○	○	●	○	○	○
Norway [223, 236] (IHSI; NPF)	NIPH[a] NMA	●	○	○	○	●	○	Technologies for specialist health care
Poland [223]	No HS system in 2019	●	●	●	●	●	●	●
Singapore [237]	ACE[a]	●	●	●	○	●	○	○[c]
Spain [223, 238] (VD)	RedETS/SINTESIS[b]	○	○	○	○	○	○	○
Sweden [223, 239] (IHSI; NPF)	Swedish EAA System (medicines only)	●	○	○	○	●	○	○

Jurisdiction (collaboration member)		1 Purpose						
		Planning	Engage Stakeholders	Engage Industry	Identify evidence limitations	Inform approaches to assessment	Review existing funding arrangements	Other
Switzerland [223] (IHSI)	No HS system in 2019	●	●	●	●	●	●	●
The Netherlands [223] (IHSI)	DHI/Horizonscan+	●	○	●	○	○	●	Innovative medicines
United Kingdom	Wales, AWTTC [240]	●	○	○	○	○	○	○
	Scotland, HIS [241]	●	●	○	○	○	○	inform on “high impact” technologies
	NICEa/NIHRa-IO [27, 242]	●	○	●	○	○	●	fast-tracking of medicines; inform NICE guidelines by licence date
USA [228]	ECRI/PCORI	●	○	○	○	○	○	○

Abbreviations: AIFA HSS = Italian Medicines Agency Horizon Scanning System; AWTTC = All Wales Therapeutics and Toxicology Centre; DACEHTA = Danish Centre for Evaluation and Health Technology Assessment; DHI = Dutch Health Institute; EAA system = early awareness and alert system; ECRI = Economic Cycle Research Institute; HPRA = Health Products Regulatory Authority; HTA = health technology assessment; HS = horizon scanning; IHSI = International horizon scanning Initiative; IMA = Icelandic Medicines Agency; IO = Innovation Observatory; MaHTAS = Malaysian Health Technology Assessment Section; MoH = Ministry of Health; NMA = Norwegian Medicines Agency; NPF = Nordic Pharmaceutical Forum; OECD = Organisation for Economic Co-operation and Development; PCORI = Patient-Centered Outcomes Research Institute; RedETS = Spanish Network of Health Technology Assessment Agencies; SINETIS = Topic identification and filtration system for Spain’s Early Detection and Awareness methods; SMC = Scottish Medicines Consortium; VD = Valletta Declaration

Notes: a. Refer to Appendix 2 for names of INAHTA Agencies

b. While Vogler reported that there were no HS activities in Spain, an abstract of an oral presentation from 2022 indicated that SINTESIS has been operating for a few years and feeding information to the Spanish Network of Health Technologies Assessment Agencies (RedETS)[238].

c. Feedback from ACE reports that preparing the health system for the introduction of new technologies is a purpose of HS, even though it is not explicitly stated

● Yes ◑ Partial ● No ○ Not reported/No information found

All jurisdictions with HS systems used HS for the purpose of planning. For example, ACE in Singapore use HS as it *"allows for better preparedness of the healthcare system by providing advance notice to policymakers and healthcare providers to aid in planning for healthcare resources allocation. It further serves to support the uptake of innovative and effective technologies while safeguarding patients from potentially unsafe technologies before its widespread adoption."* [237]

Although most HS systems engage with stakeholders and industry and have specific methods to include them in the HS process, there were no reports of this engagement being a specific goal of HS. However, the review by Vogler (2022) lists the aims of five countries in Europe that have HS in their healthcare systems. In summary the aims are to identify information about new and innovative medicines and to provide this information to the appropriate bodies and stakeholders in a timely way for planning. In Norway and Sweden an additional aim is to inform which HTA pathways should be used going forward. Italy and the Netherlands specify as goals reimbursements decisions price negotiations respectively.[223]

Other reasons for performing HS included the fast-tracking of medicines (NICE), to inform guidelines (NICE, CONITEC), to support court decisions (CONITEC), and to identify medicines for specialist health care (NMA Nye Metoder).

Summary

Although HS is undertaken with variation in the degree of systematic approaches used, the methods are similar: identify topics, filter, and prioritise them based on criteria, assess the topics and disseminate the results. Most HS systems were funded by governments or their health systems, and were performed by government bodies, or agencies representing government. Only the largest HS systems invited the input of the public or consumers for topic to be considered. A new medicine was more likely to be within the scope of a HS system if it looked likely to be of high cost or highly effective. In most cases, medicines were only considered if they were within 1 to 3 years of market approval. Planning was the main purpose reported for conducting HS, although some other reasons were also found such as informing the assessment approach, and to engage stakeholders.

Several HS systems have assessed the value of HS to their health system or government, but generally this is difficult to do, and rarely are the correct measures used. Some studies tackle evaluation by using diagnostic accuracy indicators of sensitivity and specificity, or positive predictive value and negative predictive value. For example, performance was evaluated in terms of economic impact of HS in the Swedish EAA between 2010 and 2015.[246] Of 253 new medicines identified, 71 were prioritised, and 21 were finally classified as having substantial economic impact, giving a sensitivity of 76.2% and specificity of 22.5%. However, while these evaluations provide an estimate of the function of the topic identification and filtration system, they do not indicate the impact on decision making or planning which would occur without HS. No study was

identified that successfully measured the impact on planning or preparation of the health system for a high impact medicine.

EARLY ASSESSMENT

For this paper, early assessment is subcategorised into three processes: early scientific advice (or early dialogue); early value proposition (or early HTA); and coverage with evidence development (with early value assessment as an example). The HTA Glossary does not include definitions for 'early value assessment', 'early HTA', 'scientific advice' or 'early dialogue'. It does have a definition for coverage with evidence development (CED), which is *"early funding of a health technology conditional on gathering additional evidence to address the sources of uncertainty."* [1] It is also called access with evidence development, and related terms include managed entry scheme/agreement, risk share agreement, interim funding, evidence development, conditional reimbursement, and conditional coverage.

Figure 16 illustrates the lifecycle of a health technology and when each of these types of assessment occur, along with the type of research that is undertaken. As can be seen, early scientific advice and early value proposition happen at much earlier stages of the technology lifecycle than coverage with evidence development. The timing and content of these two early types of assessment are described in more detail below. Early value assessment (EVA), as conceived by NICE, is provided as an example of a program of coverage with evidence development and is also described below. EVA occurs later in the technology lifecycle when the technology is close to regulatory approval (either just before or after).

There are also accelerated *regulatory* pathways for eligible medicines such as the EMA's early access schemes (for example PRIME and adaptive pathways), noting that these allow market access but are separate from reimbursement decision making. These schemes are designed to enable access to medicines whilst the evidence base is still developing and there is too much uncertainty around the effectiveness of the medicine to grant full reimbursement approval.

Many jurisdictions have schemes to provide early access to medicines where those medicines are for serious or debilitating conditions or address high unmet medical need but have not yet gained regulatory approval or reimbursement due to decision uncertainty. These schemes can involve the granting of regulatory approval and reimbursement under an arrangement for collection of evidence, such as NICE's Early Access to Medicines Scheme (EAMS) or the Conditional Approval for Evidence Development scheme in South Korea.

EAMS provides access to important medicines before marketing authorisation is achieved. This process occurs typically at the close of Phase III clinical trials, and approval is only given where the medicine has already been identified as a Promising Innovative Medicine. The technology also needs to be selected for NICE appraisal prior

to market access, and the appraisal begins during the access period. Notably, the medicines are provided by the company free of charge during the early access period. This scheme relies on an assurance that evidence will be provided for the NICE appraisal during the early access period and may include evidence collected during this time.[55]

The South Korean program allows medicines which address rare or severe chronic diseases, or diseases for which there are no other treatments, to be funded whilst evidence is collected. This is managed by implementing the technologies in designated institutions so that data can be properly collected and analysed.[18]

This paper describes the NICE EVA program as an example of a CED process; more discussion around CED and dealing with other types of uncertainty at the time of HTA can be found in Papers 4, 8 and 9 for the HTA Review.

EARLY VALUE PROPOSITION

Early value proposition (EVP) is used in this paper as a term to describe activities, mainly economic analyses, conducted at very early stages of technology development that help the medicine developer ascertain the potential value of their product. It is also commonly referred to as early HTA, however this is a misnomer as it does not include the usual components of HTA and does not typically inform decision-making by policy makers i.e., to promote an equitable, efficient and high-quality health system, and so do not align with the accepted definition of HTA. Thus, it has been referred to as EVP in this paper, as it better describes the purpose. As there was no standard definition of EVP or early HTA, broad search terms were used to identify relevant literature and the search returned a wide variation in the applications of EVP. Earlier articles focus on the use of economic modelling at very early stages of technology development, whilst later articles bring in other elements of HTA, especially stakeholder involvement and preferences. Evidence of EVP activities was not located on HTA agency websites; there was some reference to it but this was in a research context rather than as a routine service (such as in the Netherlands).

Most of the articles identified in the search of published literature were commentaries or descriptive papers, rather than research. There were a small number of relevant research papers identified, all systematic or scoping reviews, which are summarised below. It should be noted that most of the information on early economic analysis considers medical devices, not medicines; this research has been included in this paper as the methods are likely to be adaptable to medicine innovations.

A very recent rapid review by Rodriguez Llorian et al, (2023) investigated the frameworks used in EVP (called early HTA) assessments.[247] Although this review was

[18] Presentation by NECA, INAHTA Congress, 2023, Adelaide.

considered rapid, it was comprehensive and included articles in three languages. Studies were included if they "*provided a systematised approach in assessing the value of health technologies throughout preclinical and early clinical (phase I) stages of development*". The review identified 46 articles that described EVP frameworks. These were then classified by the authors into three categories: criteria frameworks, process frameworks and methods frameworks. The key features of each are summarised in Table 16.

Table 16 Summary of frameworks used in early value proposition articles contained in systematic review by Rodriguez Llorian et al [247]

Framework	No. of studies, years published	Topics (n)	Key features
Criteria *"identify key areas relevant for the assessment of the value of health technologies at early stages of development".*	K=11, 2008-2021	General (3) Medicines (6) Nanomedicine (1)	Identifying components of HTA that require attention at various stages of medicine development (from identifying ideal target medicines through to preparing for reimbursement applications)
Process *"provide a stepwise guide on the methodologies to follow along specific proposed levels of analysis… "levels" align directly with specific technology lifecycle stages"*	K=14 2007-2021	General (6) Tests (5) Devices (3)	Defines different stages of product development and methods that can be applied at each. Methods include consultations with experts, but predominately focus on different types of early economic analyses including headroom analysis, scenario analysis, sensitivity analysis.
Methods *Papers that focus on "one specific method to address an aspect of eHTA"*	K=20 2005-2021	General (9) Medicines (6) Devices (2) Gene therapy (1) Heart valve (1) Surgical innovations (1)	Various specific methods for specific aims such as informing product development or estimating potential cost-effectiveness in early development. Methods were mainly economic (early modelling, scenario analysis etc) but also some stakeholder consultation and estimation of effectiveness.

Abbreviations: eHTA = early health technology assessment.

This review found that there is a myriad of methods used in early HTA, noting that the "*multidimensional, cross disciplinary and multi-perspective character of eHTA reflects the complexity of the healthcare system and technology development process*". This is reflected in the lack of clear applicability of the proposed frameworks and methods to a specific timepoint in the technology lifecycle. From the included studies, the application of early HTA is somewhat ad hoc, varying from the criteria of interest to be addressed and the processes and methods used to address the criteria. Even the aims across studies vary considerably, despite all being early HTA. The authors reported that there was no evidence on the impact of this type of early HTA on innovation or commercialisation, however noted that the detail of this impact may not be published for commercial confidentiality reasons. There was no mention of how this early HTA may impact on the health system or users.

A systematic review by Ijzerman and colleagues conducted in 2017 noted that there had been four prior systematic reviews on the topic.[248] Three of these were specific to devices and found that the methods of early HTA mainly included health economic analysis, value-of-information analysis, clinical trial simulation, discrete choice experiments and multi-criteria decision analysis (MCDA), amongst others. None of the four reviews agreed on a definition of early HTA; Izjerman et al defined it as *"all methods used to inform industry and other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty''*. This was qualified by noting that industry is an important, but not the only, stakeholder; the definition includes early HTA of medical products just before and also at the early stages of clinical use; and, that early HTA not only includes early-stage health economic modelling, but also includes methods to elicit stakeholder preferences, manage risk in technology portfolios, simulate clinical trials, and identify unmet needs.

The review went on to compare methods used in the articles identified in the literature search, published after the last previous review. Twenty-two papers with explicit methods were included, and four main methods were identified. These were the headroom method, early-stage health economic modelling, methods for elicitation of stakeholder preferences and multi-criteria decision analysis. Nine studies employed economic modelling, and all but one of these studies were of medical devices or diagnostic or biomarker tests. Various models were used including Markov, deterministic and decision tree, and uncertainty was explored with various types of sensitivity and scenario analyses. The study authors noted that they were unable to estimate the impact of early HTA on the development of the medical technologies, however the authors were optimistic about the usefulness of early HTA for the future. The authors suggested that early assessment helps developers target a technology for a specific added value to society or encourages them to adapt their pricing strategy to better reflect the value that the technology brings. Additionally, they believed that the inclusion of stakeholder preferences should improve the development of technologies. However, none of these proposed benefits have been supported by evidence, and it is unclear what, if any, benefit there is to the health system as a whole from early HTA.

A study by Grutters et al (2019) entailed revisiting several early economic assessments of medical devices to see if the early assessment had been effective at distinguishing between potential cost-effective and non-cost-effective interventions (determined at a later stage).[249] In terms of the stage of development of the technology, they ranged from innovative ideas (no product yet invented) through to concept development, pre-market and at market access, so with considerable variation in the amount of evidence available for the analysis. Different types of economic analysis were therefore applied, from headroom analysis through to preliminary standard cost-effectiveness analysis with some threshold/scenario analysis. The authors found that all the technologies had the *potential* to be cost-effective, due to health gain, cost savings or both. After the EVP was undertaken none of the analyses resulted in a firm no-go position for launching the technology. This seems hardly surprising, given that few of the included parameters

were certain or factual, and the ability of the technology to perform (or for the company to price accordingly) at the hypothesised levels to be considered cost-effective was unknown. However, nearly all assessments included recommendations on where further development or implementation should be focused. For most technologies, this was in the positioning of the technology in the care pathway and in the value proposition to the technology sponsor. Further research was also recommended for most technologies, and most of this focused on defining the value proposition. This is unsurprising given that many of the technologies were in a stage of development with very little clinical evidence to inform the analysis. No follow up of the impact (or predictive power) of the early economic analysis was included in the research. The authors concluded that early economic analyses using scenario analysis could help evaluators and industry understand the uncertainty in the evidence base and provide insight into how to proceed with technology development.

A systematic review by Smith et al (2019) examined the clinician's role in EVP.[250] This study noted in its background that EVP was very beneficial to the developer in terms of optimising research and development process flow, device design features, ergonomic factors, user perspectives, reimbursement potential and cost effectiveness, at a point in development when it is affordable and technically feasible to implement changes. In terms of the benefit to payers and health systems, they note that EVP may help resource allocation by helping to identify technologies which would be beneficial to society at an early stage, whilst diverting attention away from unhelpful technologies. The review included 33 studies which mentioned the role of the clinician in EVP and found two major areas where the clinician was involved: needs based problem solving, such as describing clinical, user and manufacturer's needs; and conformity assessment, including device performance and safety, and study design. Minor themes were contribution to economic evaluation and managing conflicts of interest. The authors suggested that clinician input in these areas could occur across technology development from basic research on the mechanism through to prototype product development. The authors of this study also noted that there has been no research into the benefit or cost effectiveness of EVP itself.

A scoping review by Grutters et al (2022) examined the methods used in EVP to explore the value of health technologies to patients and society.[251] Six reviews were included, and 43 different methods were identified. The authors grouped these into four classes according to their goal. The classes were:

(1) methods for exploring the nature and magnitude of the problem.
(2) methods for estimating the nature and magnitude of the (societal) value that may be expected with the use of the technology.
(3) methods for identifying the set of conditions that need to be met for the potential value of a technology under development to materialise.
(4) methods to help develop and design the type of research needed to demonstrate the expected value.

They also found other generic methods that could be used for each goal, including quantitative modelling techniques and qualitative methods for engaging stakeholders. This scoping review describes methods than can be used in EVP, but like the other articles identified, does not explore the impact or benefits of EVP to the health system.

Some specific examples of early economic modelling and EVP were identified in the literature search; most were related to medical devices rather than medicines. However early economic modelling has been used in some pharmaceutical or advanced therapy indications such as mesenchymal stem cell therapy for septic shock [252], personalised medicine [253] and predictive biomarkers in breast cancer. [254]

Overall, the use of EVP is primarily to support the technology developer, who can use the findings to inform product development and marketing. This has the potential to have a massive impact on the return on investment for the company, including avoiding investing in a technology that might not clear marketing or reimbursement hurdles. However, these potential benefits have not been quantified in the available research. The benefits to other stakeholders, particularly payers, are hypothetical at best. As with ESA, advantages may flow on to patients (who are able to convey important information about disease states, quality of life and value of treatments). Benefits could be accrued by the health system if the EVP resulted in the development of technologies that address unmet need and have the best chance of having a positive impact on health. However, given that EVP is not undertaken in a systematic way across any jurisdiction globally, and is optional on the part of the developer, it is unlikely that system-wide effects would be manifested. There was no evidence identified that could show benefit or the value for money associated with EVP, for any stakeholder.

EARLY SCIENTIFIC ADVICE

Early dialogue or early scientific advice (ESA) (not defined in the HTA Glossary) are services provided to industry at early stages of medicine development. The European Network for Health Technology Assessment (EUnetHTA) defines early dialogue as *"non-binding scientific advice, before the start of pivotal clinical trials…in order to improve the quality and appropriateness of the data produced by the developers in view of future HTA assessment"*.[255] The terms early dialogue and early scientific advice are used interchangeably and ESA is used hereafter.

ESA is an established service across many jurisdictions, especially in Europe. ESA can include regulatory and HTA advisory perspectives, and increasingly, these can be accessed in parallel. Table 17 shows the key features of ESA provided by agencies identified in the search. Note that other agencies are likely to provide this service, but this could not be confirmed because information in English was not available. In Australia, ESA as provided by the TGA is available only for products seeking a biowaiver justification. No other evidence of the provision of ESA in Australia, via TGA or PBAC, was identified, apart from the results of the pilot process discussed further below.

Table 17 Summary of early scientific advice activities across regulatory and HTA agencies

Country/ region	Agency	Optional or compulsory Binding or non-binding	Initiated by	Timing of advice	Advice content	Cost	Providers of advice	Parallel ESA options	Time to advice
Europe ESA made publicly available after medicine obtains marketing authorisation	EMA[256]	Optional Non-binding	Developer	Any stage of medicine development (designed for access to market ie regulatory)	Quality (eg manufacturing); non-clinical (eg toxicology); clinical; methodological; overall development strategy Also protocol assistance for developers of designated orphan medicines	Fee for service; reductions for orphan medicines and SMEs Full waiver for medicine intended to treat, prevent or diagnose a public health emergency	Scientific Advice Working Party, comprised of various members of other committees (such as Committee for Orphan Medicinal Products) and clinical, non-clinical, methodological and therapeutic experts; patients	FDA EUnetHTA HTA bodies	Approx. 3 months
Europe[a]	EUnetHTA Early Dialogue[255]	Optional Non-binding	Developers Topics selected based on innovation, seriousness of the disease and unmet need	Before pivotal studies	Clinical and economic; provides advice that is consistent across all European Member states, or highlights where this is not possible	Fee for service depending on agency	Individual HTA agencies on behalf of EUnetHTA; clinical experts; patients	EMA	2.5-3.5 months
Europe National scientific advice from more than one country at a time	EU Innovation Network in conjunction with EMA clinical trials accelerat'n unit	Optional Unclear	Developers, academic research centres and hospitals	Still in pilot phase: focus on timing for before clinical trials (any phase) but entire life cycle of technology in principle	Advice specifically related to conduct of clinical trials	Fee for service	Two national agencies, can be requested. Other stakeholders not mentioned	Unspecified	3 months
France *Unclear if reimbursement*	HAS[257]	Optional Non-binding	Developer	Before pivotal studies	Medical, medico-economic	Unspecified	HAS staff, clinical experts, patients	Parallel with EMA undertaken	110 days for standard procedure;

Country/ region	Agency	Optional or compulsory Binding or non-binding	Initiated by	Timing of advice	Advice content	Cost	Providers of advice	Parallel ESA options	Time to advice
committees have access to ESA[b]				(generally phase III trials)				through EUnetHTA	75 days for accelerated procedure
Canada *Reimbursement committees do not have access to ESA*	CADTH (parallel Health Canada process includes INESSS as observer)[258]	Optional Non-binding	Developer	Before pivotal trials	Clinical and economic	Fee for service	CADTH staff, clinical experts, health economics expert, patients, possibly a past member of reimbursement committees	Health Canada (regulator); NICE UK	18 weeks for standard process, and parallel process with Health Canada (regulator); 20 weeks for parallel process with NICE
UK *ESA not shared with any appraisal committee*	NICE[259]	Optional Unspecified	Developer	Pre-clinical/ Phase I; Phase II and III; post phase III, pre-authoris'n; post-authoris'n	Clinical and economic Also a specialised service for advice on an economic model	Fee for service	Clinical, health economic and HTA experts; patients	MHRA CADTH Concurrent with but separate to EMA ESA	15-17 weeks from submission of briefing book
Italy	Italian Medicines Agency[260]	Unspecified Unspecified	Developer	Before market entry but no further details available	Quality, safety and efficacy and may extend to HTA issues (not specified)	Fee for service	Unspecified	Unspecified	3 months
Netherlands	Medicines Evaluation Board[261]	Optional Unspecified	Developers - industry or academia	Entire product cycle	Quality, pre-clinical, clinical	Fee for service	Experts- no further details provided. Advice signed off by President of the Board and National Scientific Advice Coordinator	ZIN (National Health Care Institute or reimbursement) ZIN also provides scientific advice but details could	7 weeks

Country/ region	Agency	Optional or compulsory Binding or non-binding	Initiated by	Timing of advice	Advice content	Cost	Providers of advice	Parallel ESA options	Time to advice
								not be identified	
Germany	Federal Joint Committee (decision maker; overseer of physician, hospitals and health insurance funds)[262]	Presumed optional but unclear how related to compulsory early benefits assessment	Developers	Early- before pivotal trials, or late, to offer advice on requirements for early benefit assessment	Unclear but includes advice on PICO and study design	Fee for service	Working group not further defined	Medicines Evaluation Board	8 weeks
Sweden *Unable to find details in English; participates in EUnetHTA*	Dental and Pharmac-eutical Benefits Agency	Presumed optional but conjoint regulatory advice is mandatory Unspecified	Developers	Unspecified	Clinical, health economics	Fee for service	Unspecified	Unspecified	Unspecified
Sweden	Swedish Medical Products Agency[263]	Unspecified Non-binding	Developers	Advice for clinical testing or marketing authoris'n	Non-clinical, clinical, statistics, pharmacokinetics, quality	Fee for service	Unspecified	Unspecified	Unspecified
Spain	Spanish Agency for Medicines and Medical Devices[264]	Unspecified Unspecified	Developers	Focus on development strategies	Quality, non-clinical, safety, clinical, pharmacovigilance, regulatory requirements	Fee for service	Unspecified	Unspecified	90 days
USA	FDA[265]	Optional Non-binding	Developers	Multiple time points in medicine development	Various aspects depending on reason for request; several types of advice available	Unspecified	FDA staff, no further detail available	EMA Unclear if FDA advice has been superseded by parallel SA	Advice meeting within 30-75 days of request, depending on type

Abbreviations: EMA = European Medicines Agency; SA = scientific advice; FDA = Food and Drug Administration (USA); EUNetHTA = European Network for Health Technology Assessment; CADTH = Canadian Agency For Drugs and Technology in Health'; INESS = Institut national d'excellence en santé et services sociaux; UK = United Kingdom; NICE = National Institute for Health and Care Excellence; MHRA = Medicines and Healthcare products Regulatory Agency; PICO = Population, Intervention, Comparator, Outcomes

Notes: a. Note this service is ending in September 2023 and EUnetHTA will no longer coordinate parallel assessments, however these are still available via EMA in accordance with a new EU HTA regulation

b. No one providing the advice is allowed to both prepare ESA and participate in future assessments of the technology

A systematic review of ESA frameworks was identified in the search [101] but this did not provide additional information to that provided in the table above.

A pilot study of parallel ESA provided in Australia by the TGA and PBAC was conducted in 2009 for two different medicines.[266]The method included the provision of briefing books to the TGA and PBAC, and a series of questions from the pharmaceutical company, which were then addressed in a two-hour meeting between the three parties. The parties were then asked to comment on the process. The TGA and PBAC contributors noted that whilst the meeting was worthwhile, it was too resource-intensive to offer on a regular basis to all companies who requested it without considerable investment. On the other hand, the company found the advice given to be both constructive and actionable, and helped them to prioritise issues.

Overall, the scientific advice provided by regulatory or HTA bodies across the world is similar in that it is optional, operates on a fee-for-service basis and is non-binding on both parties. Timeframes varied by agency, but most fell into the 3–4-month timeframe. Most agencies offered advice prior to the design of the pivotal clinical trials, which allows for the opportunity to modify key aspects of the study. This helps developers ensure study design and execution, including the PICO criteria, are optimised for market access and for HTA. Scientific advice at this point of medicine development is also key to ensuring patient perspectives are included in trial design and other aspects of evidence collection. This applies particularly to how trials are executed, which may help with recruitment, and to the prioritisation of outcomes that are of the most relevance to patients. Patient perspectives at this point also help HTA agencies understand the health issue as it currently exists, and what the new medicine may value-add.

There has been movement towards parallel ESA across regulatory and HTA agencies, and across jurisdictions and countries. This is advantageous to the medicine sponsor, who can ensure that the evidence collected will satisfy the requirements of both regulation and reimbursement and lessen the workload of the sponsor who may wish to apply for approval in more than one country. It also makes sense for regulatory and HTA agencies not to duplicate the advice service, noting that there may be some differences across health care settings (such as comparator treatments available) that could mean conflicting advice is provided to the sponsor. A study by Gailbraith (2022) of multi-agency HTAs conducted under the auspices of EUnetHTA noted that finding clinical experts with experience across international settings was difficult, and that their advice was necessarily limited to single countries. This may be a limiting factor for ESA that crosses national or even jurisdictional boundaries. This could apply to the patient experience as well.

A study by Wang (2022) investigated the impact of early advice on trial development through a survey of industry.[267] The study found that 58% of development plans were changed based on parallel advice from regulatory and HTA agencies, compared with 46% of plans which received HTA-only advice, and 25% of plans that received multi-HTA agency advice (through EUnetHTA). However, it should be noted that development plans

that were not changed also included those in which it was unknown if there were changes. A study of the impact of NICE ESA conducted by Maignen was only presented as a conference abstract and so not technically included in this review, however as little information was identified that examined the impact of scientific advice, the results are provided here.[268] This study found that of 341 advice products provided between 2009 and 2019, only 44 went on to receive marketing authorisation. The abstract does not explain what happened to the other medicines that received ESA. However, of the 25 products that had completed a full NICE HTA, all were recommended. Importantly, the study also noted that the time between market authorisation and publication of NICE guidance was 296 days for the products that received ESA, compared to 405 days for the products that did not. A study of marketing authorisation applications to the EMA that received scientific advice (either before or during pivotal trials) was published in 2015.[269] This study found that products that had received and complied with scientific advice had a higher rate of success with their applications. Notably, 63% of applications which were deemed to be unacceptable for marketing authorisation application at the time of scientific advice modified their trial design. Another study of parallel advice provided by the EMA and HTA bodies compared the advice given with the actual clinical study that resulted.[270] The study found that advice on comparators from the regulator and at least one HTA body was followed in 12 out of 21 studies, whilst seven studies followed the regulatory advice only. In two studies, no advice was adopted. For the primary endpoint, all included studies implemented the recommendations of the regulator and at least one HTA body. None of these studies provided evidence to demonstrate benefits to the HTA process, patients or the health system more broadly.

It appears that the benefits of ESA flow predominantly to the sponsor, in that the advice is used to optimise their medicine development and aid a smooth transition through regulatory and reimbursement requirements. Additionally, it may save them the cost of investment in a technology that is not suitable for the patient or health system. The advice may also help maximise trial recruitment, by incorporating patient preferences. There is also a flow-on effect for patients, whose influence on medicine research can ensure it meets their needs and reflects their priorities. The benefits to regulatory and HTA agencies are less obvious, except those from the fee-for-service model. It is theoretically possible that if the advice is followed by the sponsor that it will ease the process of evaluation, in that there should be better quality applications, but there was limited evidence to confirm this. The increasing trend of parallel ESA and sharing across jurisdictions does provide some opportunities for efficiency and, perhaps, swifter funding decisions. Whether this results in faster funded access to medicines by patients remains to be seen and would be largely dependent on the health system (see Paper 4c).

EARLY VALUE ASSESSMENT

EVA has been included in this paper as it has recently been adopted by NICE as a process for accommodating *"quicker access to promising health technologies that address national unmet need".*[271] This process was begun in late 2022, and although it relates to medical devices, digital products and diagnostics only in the UK, the HTA Review Reference Committee have asked that it be considered as a model in this paper. It is an example of a CED scheme.

This type of assessment is intended to guide the NHS on which new technologies, particularly digital technologies, will make a real difference to patients. It occurs at a point in the technology life cycle similar to traditional HTA, in that the technology must have regulatory approval and already be in use (or expected to be in use in the next six months), but without a sufficient evidence base to undergo traditional HTA. No other agencies were identified that undertook assessment at this time, with the same criteria.

In EVA, like HS, topics are identified, filtered and assessed. The key driver for NICE EVA is to match new technologies to priority areas in health and social care, which address a clinical, system or service user problem identified by NHS England and through stakeholder engagement. Whilst the process is in its early stages, the pilot projects have been allocated 8-16 weeks for scoping and 4-20 weeks for assessment, varying depending on the project [175].

Completed EVA reports are then passed to a decision-making committee, who decide if the technology should be approved for early use in the NHS and under what conditions (such as the type of evidence that will need to be generated). The technology will then be later re-assessed through a full NICE HTA report.

Germany has a process called 'early benefit assessment' which considers medicines once they have regulatory approval.[272] The process is overseen by the Federal Joint Committee (G-BA) of the German Statutory Health Insurance (SHI) system. Every new medicine undergoes this assessment, and the pharmaceutical company must provide a dossier containing information relevant to the PICO criteria for the intended use, and all the relevant clinical evidence, including a systematic search, for the medicine. The company's dossier is then assessed by the Institute for Quality and Efficiency in Health Care (IQWiG), an HTA agency. This occurs three months after market entry. External experts and patient representatives are asked to provide input prior to the assessment. The assessment focuses on patient-relevant outcomes, and once the evidence has been assessed, a conclusion is made on the degree of certainty of the conclusions, and the extent of any added benefit related to the medicine. This conclusion is fed back to the Federal Joint Committee who then make a final decision on the medicine. This decision informs three major stakeholders: the SHI who use the information to negotiate on price with the company; physicians, who can quickly access the evidence via an electronic information system and where the evidence is included in a clinical practice

guideline; and patients who are able to access the information in an easy-to-understand format.

Whilst this is called an 'early benefit assessment', this does not really qualify as early in comparison to the NICE EVA. Whilst they are similar in that the technology is already market approved, the purpose of NICE EVA is to identify important technologies that address specific health priorities or address unmet need and that do not have an adequate evidence base for a full HTA. This is to facilitate early access and to provide guidance for the ongoing evidence collection. In contrast, the German system considers every new medicine that has been approved by the regulator, and the evaluation most closely resembles the clinical assessment part of a traditional HTA (as undertaken in Australia). This is exemplified by the comprehensive content of the required company dossier and the expectation that the evidence base is enough to show added benefit of the medicine over standard care.

Early value assessment: process

The EVA process sits within NICE and is therefore closely related to government priorities, including topic selection and assessment. Internal and external stakeholder engagement is key to the identification, selection and validation of appropriate topics. Stakeholders are involved in topic selection across healthcare policy (to ensure alignment to policy drivers), reimbursement, clinical expertise (including clinicians, patients and academia) and technology expertise (including industry). The process by which topics are identified and validated as priorities is called topic intelligence, and its key aims are to:

- *"develop networks to generate intelligence streams on key topic areas to better understand system priorities (service or clinical needs).*
- *proactively scan for devices, diagnostics, and digital health technologies which meet system priorities.*
- *carry out targeted engagement with the wider system to confirm the right topics are being considered for various work programmes, helping NICE to focus resources on the most impactful outputs."* [175]

Early value assessment: Scope

The primary target of the NICE EVA program is technologies that address national unmet need. The three domains that are considered in topic selection are clinical, system or service user needs, identified through strategic engagement with the health and care system; health and care policy priorities established and validated through engagement with key policy teams; and suitable technologies which are systematically searched from a variety of sources and filtered for evaluation by NICE.

Whilst EVA was initially conceived to address the speed and quantity of digital technologies entering the market, it is not limited to these technologies. The pilot topics undertaken so far are:

- Digitally enabled therapies for adults with anxiety and adults with depression;
- Point of care testing for urinary tract infections to improve antibiotic prescribing;
- Guided self-help digital cognitive behavioural therapy for children and young people with mild to moderate symptoms of anxiety or low mood;
- Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies (a near to patient test that provides a result quickly to avoid contraindicated antibiotics).
- ProKnow cloud-based system for radiotherapy data storage, communication and management (a system that allows collaboration and peer review of treatment plans)
- CaRi-Heart for predicting cardiac risk in suspected coronary artery disease (medical imaging analysis software that uses artificial intelligence to analyse images from CT coronary angiography)[273]

A further nine technologies currently in consultation all focus on digital technologies such as artificial intelligence-aided treatment and diagnosis and digital aids to therapy across different indications.

The technologies considered by NICE for EVA are market-approved and are either already in use in the NHS or are expected to begin uptake in the next six months.

Early value assessment: Purpose

The key purpose of this new type of HTA used by NICE is to:

> *"improve the care of people and effective use of NHS resources through quicker access to promising health technologies that address national unmet need. It champions stronger partnership working between regulatory, healthcare and research organisations to benefit people and better support innovators while ensuring value for money for the NHS."*

The process has four key aims, which encompass prioritising innovations that meet needs, enabling earlier access, supporting evidence generation and ensuring that benefits are realised and value for money is obtained.

The provision of an evidence generation plan is a key output of the EVA process, as technologies approved for early access under EVA will need to progress to full NICE HTA evaluation in the future.

PATIENT ENGAGEMENT IN HS AND EARLY ASSESSMENT

There is an opportunity to genuinely involve patients in HTA at meaningful timepoints across the technology lifecycle, and agencies that undertake HS and some form of early assessment have documented processes for this. These are summarised below. Note that there is a considerable body of work that pertains to patient engagement in HTA as a whole; much of this was not identified in the search, as the search was specific to HS and early assessment. Only those agencies that specifically include patients in their processes for HS or early assessment, and articles identified in the literature that report the same, have been included here.

EVIDENCE FROM DOCUMENTS PRODUCED BY HTA AGENCIES

Five HTA organisations (CADTH, All Wales Therapeutics and Toxicology Centre (AWTTC), NICE, NIHR and EuroScan) made explicit reference to patient engagement within the context of HS and early assessment (Table 18). In contrast to the documents by CADTH, AWTTC, NICE and NIHR, which reported on practices adopted in their jurisdictions, the EuroScan document is a toolkit for use by countries that maintain or want to develop their own HS or EAA system. As such, it is a resource for adopting and adapting a HS methodology to a jurisdictional context, rather than any one methodological example established by a country undertaking HS and/or early assessment. Organisations that were identified as undertaking HS and/or early assessment but did not report patient engagement as part of these HTA activities are not discussed further.

Limited information was reported on the types of technologies considered in the identified agency documentation, and organisations commonly reported that their HS and/or EA activities targeted new and emerging technologies, without further specification. For the six HTA organisations that produced documents with explicit reference to patient engagement as part of HS and/or early assessment, the range of technologies covered were medicines, devices, tests, procedures and programs, as described by CADTH [227], while the AWTTC 2017 (Wales) described undertaking medicines-specific HS and early assessment with patient engagement.[240] EuroScan (now i-HTS) proposed options for potential scope for new and emerging technologies, where those utilising the EuroScan toolkit may consider eligible technologies from among the categories of medicines, devices, diagnostics, surgical interventions, medical procedures, hospital care, community care/programs and public health interventions. NICE defined eligible technologies within a broad scope including devices, diagnostics, interventional procedures, medicines, combination or integrated technologies, and human tissue products.[274] NICE also has a program dedicated to highly specialised technologies. Specific criteria are provided which centre on very rare or very severe

diseases, where special considerations are required.[274] The NIHR (UK) defined their HS scope as innovative medicines, devices, diagnostics and digital technologies.[242]

Methods for patient engagement in HS and/or early assessment were poorly described across the organisations in Canada, Wales and the broader UK, while EuroScan provided specific recommendations for approaches to patient engagement in HS. Of the early assessment methods previously described, NICE was the only organisation to have used one (EVA). The range of methods recommended by EuroScan (2014) for patient engagement in the HS process included patient questionnaires, interviews and focus groups. CADTH reported that Canadian patients are provided direct access to the Horizon Scanning Product Development team, who may be contacted with suggestions for HS topics.[227] CADTH reported that Canadian patient representation groups provide input to the CADTH Common Drug Review and the CADTH pan-Canadian Oncology Drug Review, liaising with CADTH to identify patients with relevant expertise to contribute scientific advice, advise on optimal use, and contribute to environmental horizon scans. Recommendations on medicines and medical devices are made publicly available with details on how patient perspectives have contributed to the conclusions. However, insufficient discussion was provided to determine the specific method(s) for gathering this patient information in the Canadian context.

In Wales, the Patient Access to Medicines Service (PAMS) is responsible for identifying relevant patient organisations, and pharmaceutical companies are requested to identify relevant patient organisations on their submission forms.[240] The AWTTC's open process of patient engagement was established in 2002 and patients, carers and patient organisations are given the opportunity to outline their experience of the relevant clinical condition and treatments, after which appraisal committees are informed of these patient perspectives. However, while the type of contribution made by patients to the AWTTC's HS/early assessment processes was clearly defined, specific modalities of engagement (e.g., interviews, questionnaires, meetings, focus groups) were not discussed. Similarly, while the NICE documents did not provide information on specific methods of patient engagement for their EVA program, discussion on the types of contributions and the intended purpose of gathering information from a patient perspective was detailed. NICE identified that patient contributions are considered useful for feedback on the placement, potential value, feasibility, acceptability and implementation of a given technology, and that patients may provide a role in reviewing evidence generation plans around feasibility and appropriateness considerations for the technology.[274] Similar to the Canadian context, NICE reports that members of the public may contribute by suggesting topics for NICE health technology prioritisation.

Table 18 Patient engagement in HS or early assessment documented by HTA agencies

Guidance document and agency	Is evidence for horizon scanning and/or early value assessment methods provided in the document?	Documented approach to patient engagement in HS and/or EA	Clinical context for HS and/or EA? Technology context for HS and/or EA.	Methods for patient engagement
HORIZON SCANNING AND EARLY ASSESSMENT				
UK				
AWTTC[a240]	HS: Y Pharmaceutical companies are expected to make an initial submission to AWMSG before receiving MA for their product and this early identification is assisted by horizon scanning. The initial submission provides the information required by the AWMSG Steering Committee to decide whether the medicine requires appraisal by AWMSG (AWTTC 2017, p.2) EA: Y AWTTC 2017, p.6 states: If there is sufficient evidence to demonstrate clinical and cost effectiveness, then an early HTA would always be the preferred approach	AWTTC reports that the AWMSG engages a variety of stakeholders, including patient interest groups and lay representatives in an open and transparent manner This open process was established in 2002 to prioritise the assessment of new medicine submissions (AWTTC 2017, p.2)	Medicines	AWTTC 2017, p.2 states: *"PAMS undertakes a search to identify relevant patient organisations, and pharmaceutical companies are also asked to list relevant patient organisations on their submission forms. Patients/carers/patient organisations are invited to outline their experience of the disease/condition in question and any experience they might have of the associated treatments; the appraisal committees are informed of the patient perspective."*
NICE[a274]	HS: Y EA: Y (by inference of the medical technology prioritising focus described)	NICE 2022 Section 3.1 states: Topics that meet the priorities of the health and care system are identified from a range of sources including: suggestions emailed to NICE's topic selection team (topic.selection@nice.org.uk) from anyone including health and care staff and members of the public	Medical technologies addressed according to identified areas of priority and information from a variety of stakeholders. There is also a dedicated programme for highly specialised technologies.	Section 5.1 notes that patients may be engaged in the briefing process once an eligible topic has been determined. The specific methods of engagement are not described. Section 6.3.1 states that one of the criteria used in the selection of a device, diagnostic, digital technology, combination technology or integrated topic for assessment is advice from stakeholders, including patients, that the potential benefits are meaningful and likely to be realised when adopted in the UK health and care system.

Guidance document and agency	Is evidence for horizon scanning and/or early value assessment methods provided in the document?	Documented approach to patient engagement in HS and/or EA	Clinical context for HS and/or EA? Technology context for HS and/or EA.	Methods for patient engagement
HORIZON SCANNING				
Canada				
CADTH[a] (HS-specific)[227]	HS: Y EA: N	ND	CADTH 2017 p.7 states CADTH's HS purpose as: Identify and evaluate the evidence on new or emerging health care technologies that may be important. This is inclusive of medicines, devices, tests, procedures, programs (p.8).	CADTH 2017 p. 11 states: *"Patients, and clinicians can suggest topics to the Product Development team directly or by emailing: HorizonScanning@CADTH.ca."*
CADTH[a] (HTA general)[275]	HS: Y EA: N	ND	ND	CADTH 2022, p.3: *"Citizen councils can be used to identify values of the population who use health care (as patients) and who ultimately provide it (as taxpayers).* *Canadian patient groups share the diverse perspectives of their communities with CADTH via patient input to the CADTH Common Drug Review and the CADTH pan-Canadian Oncology Drug Review, and liaise with CADTH to identify patients with specific expertise to contribute to Scientific Advice, Optimal Use, and Environmental and Horizon Scans. Drug and medical devices recommendations publicly detail how patient perspectives were considered to reach conclusions."* These findings are applicable across the full CADTH HTA context, including HS.
International				
EuroScan[b219]	HS: Y EA: N	EuroScan 2014, p.15: Identification can be: Proactive: where a range of sources are searched for information on new and emerging health technologies. Reactive: where systems are in place that allow stakeholders, health professionals, developers and/or consumers to inform the	New and emerging health technologies, including medicines, devices, diagnostics, surgical interventions, medical procedures, hospital care, community care/programs and public health interventions.	Patients and patient groups are listed at item 10, stage 5 of the EAA system checklist (EuroScan 2014 Appendix 8) EuroScan 2014, p.28 states that stakeholders, including patients or their representatives, may be engaged in the external review process, for the purpose of checking accuracy of data and information as well as further input and amendments prior to publication.

Guidance document and agency	Is evidence for horizon scanning and/or early value assessment methods provided in the document?	Documented approach to patient engagement in HS and/or EA	Clinical context for HS and/or EA? Technology context for HS and/or EA.	Methods for patient engagement
		EAA system on new and emerging health technologies.		All stakeholders, including patients may be engaged via questionnaires, interviews and focus groups (EuroScan, p.34). Patients/patient representatives are included in stage 7 of the EAA checklist as a potential sources of peer review.
UK				
NIHR[a242]	HS: Y EA: N	This is a presentation of the National Institute for Health Research Innovation Observatory. Slide 8 identifies core activities of the NIHR Innovation Observatory – one of these is patient and public involvement through VOICE.	The title of the presentation defines the scope as innovative medicines, devices, diagnostics and digital technologies.	Methods of engagement are not described; no information other than to identify public involvement as part of the NIHR HS process.
EARLY ASSESSMENT				
UK				
NICE[a] Early Value Assess-ment (EVA)[175]	HS: N Early Value Assessment (EVA): Y	Document is NICE EVA interim statement, which states in section 4.1: The early value assessment evidence generation approach is designed to help technology developers to work with patients and clinicians, along with NHS data custodians and analytical partners who can generate the new evidence needed either from new or ongoing research or from real-world data.	New and emerging medical technologies addressed according to identified areas of health and social care.	Methods of patient engagement not defined. Section 4.6 of the document states that stakeholder input, inclusive of patient contribution, will inform EVA by: *"Providing the technology developer with relevant and constructive contributions, based on their experience, expertise, and knowledge to influence the evidence generation plan. These contributions could include feedback on the placement of the technology, its potential value, its acceptability or feasibility and its implementation. They could also incorporate reviewing any potential evidence generation plans around their feasibility and appropriateness."*

Abbreviations: ATMP = Advanced Therapy Medicinal Product; AWMSG = All Wales Medicines Strategy Group; EA = early assessment; EAA = early awareness and alert; EVA = early value assessment; HS = horizon scanning; HTA = health technology assessment; JSC = Joint Scientific Consultation; N = no; NA = not applicable; ND = Not defined; PAMS = Patient Access to Medicines Service; VOICE = Valuing Our Intellectual Capital and Experience; Y = yes.

Notes:

a. Refer to Appendix 2 for names of INAHTA Agencies

b. EuroScan; now i-HTS – International HealthTechScan

EVIDENCE IDENTIFIED IN THE LITERATURE SEARCH

Nine publications were identified through literature searching which reported on patient/consumer engagement in the context of HS or early assessment. Four of the nine publications reported information on HS and/or early assessment which converged with evidence of patient involvement in the HS and/or early assessment processes.[276-277-279] Table 11 provides a summary of the four publications according to inclusion of information on HS and/or early assessment, information on patient engagement and whether the publication discussed patient engagement within the context of HS and/or EVA specifically. Two of the articles indicated an early assessment was involved – one performed early HTA (also called EVP) and in the second, early assessment was inferred from the methods reported in the study (early assessment method was not clear).

The clinical and technology contexts captured across the four papers were varied. The studies included an early pharmaceutical HTA by the Scottish Medicines Consortium (SMC) specific to end-of-life, orphan and ultra-orphan medicines [276]; a UK technology priority setting exercise using patient perspectives in the context of faecal incontinence [277]; a case study of a UK EAA system (NIHR) drawing on EuroScan guidance to engage patients and the public in the identification, filtration, prioritization, early assessment, and dissemination stages of health technologies [278]; and a US report of an HS process for patient engagement on HS topics pre-selected as potentially highly disruptive for healthcare systems.[279]

Surveys were the most common method used to engage patients in the HS and/or early assessment process. Three of the four papers included for analysis reported the use of surveys for patient engagement [277-279]. Among the studies that used survey approaches, there were differences in the platforms and mechanisms used to survey patients, and not all three studies that used surveys used them exclusively. O'Connor et al reported that following their international survey to gather perspectives of patients to inform UK HS priority setting in the context of faecal incontinence, the same patients were followed up with an online workshop using a range of modalities (focus group discussions, online polling and ideation/consensus techniques).[277] Similarly, Simpson et al also used focus groups alongside contact by email, telephone, and use of a website portal and Twitter to obtain patient perspectives for the UK NIHR EAA system.[278] Tipton et al, operating from a US context, engaged patients by surveys and standardised review forms after patients had participated in the review of online content consisting of reports and video on the pre-selected HS topics.[279]

Workshops with HTA bodies in 2019 identified several methods for patient engagement in ESA which may vary according to the form of ESA sought by a medicine developer. For example, if it is a parallel advice with a regulatory body such as EMA, the EMA

process will be used. The two main approaches are interviews and attendance at multi-stakeholder meetings.[19]

[19] PARADIGM Patient Engagement in Early Dialogues: Tools and resources for HTA bodies: https://imi-paradigm.eu/petoolbox/pe-in-ed-hta/ Accessed 28 Sept 2023

Table 19 Patient engagement with HS or early assessment identified in the literature search

Study	Does the publication discuss horizon scanning and/or early value assessment?	Documented approach to patient engagement in HS and/or EA	Clinical context for HS and/or EA? Technology context for HS and/or EA	Methods for patient engagement Findings
HORIZON SCANNING AND EARLY ASSESSMENT				
O'Connor et al (2023) [277]	HS: Y EA: Y; (inferred from study methods)	This study reports on patient and public involvement in a project to identify priority topics and uncertainties for future systematic review questions. It involved key international faecal incontinence stakeholders, alongside horizon scanning methodology and literature searching.	Clinical context: faecal incontinence. No specific emerging technologies were discussed in the paper.	A range of stakeholder perspectives in the context of faecal incontinence, including those of patients and their carers, were used alongside HS techniques to assess emerging (early/pipeline) evidence. The methods to gather these stakeholder perspectives were an international survey followed up with an online workshop where ideation techniques, focus group discussions, consensus techniques, and online polling were used to expand and refine findings. The authors concluded that: *"This project successfully followed robust methodology, building upon frameworks from published priority setting and evidence gap mapping projects while incorporating strong patient and public involvement components."*
HORIZON SCANNING				
Simpson et al (2018) [278]	HS: Y EA: N	The study reported on experiences, benefits, and challenges with PPIE from a publicly funded EAA system in the UK.	Technologies, not further defined, as identified by the National Institute for Health Research Horizon Scanning Research and Intelligence Centre EAA system.	Email, telephone, a Web site portal, Twitter and focus groups were used to engage patients and the public at various stages of an EAA system, as recognised by EuroScan (EuroScan 2014; see Table 9): identification, filtration, prioritisation, early assessment, and dissemination. The authors reported that PPIE were successfully integrated into all aspects of the NIHR Horizon Scanning Research and Intelligence Centre's EAA system. Input was most beneficial in the areas of prioritisation and early assessment. Valuable insight was provided on the Centre's Web site and engaging patients using Twitter has enabled the Centre to disseminate outputs to a wider audience.
Tipton et al (2020)[279]	HS: Y EA: N	The study presented findings from the patient engagement process used by the PCORI Horizon Scanning System.	Specific examples of clinical and technology contexts for HS topics in which patients were involved are discussed in the study.	Patients were surveyed and providing with a standardised review form after viewing online content (written reports and video) presenting a range of potential HS topics with high disruptive potential for healthcare systems. Study findings were reported as follows:

			Examples included pharmacological treatments across clinical areas of cancer, Alzheimer's disease and rare diseases, and devices used in the care of cardiovascular conditions.	54 patients and caregivers were invited to participate; 39 reviewed at least one report. These perspectives informed analyst nominations for 14 topics in two 2019 High Potential Disruption Reports. 34 patient stakeholders completed the user-experience survey. Most agreed (68%) or somewhat agreed (26%) that they were confident they could provide useful comments. 94% would recommend others to participate. *The authors concluded that:* *"The system has successfully engaged patients and caregivers, who contributed unique and important perspectives that informed the selection of topics deemed to have high potential to disrupt clinical care. Most participants would recommend others to participate in this process. More research is needed to inform optimal patient and caregiver stakeholder recruitment and engagement methods and reduce barriers to participation".*
EARLY VALUE ASSESSMENT				
Hems et al (2023) [276]	HS: N EA: Y; early HTA conducted by SMC on behalf of NHS Scotland	Study clearly reports that patients are included in the early HTA process via PACE meetings.	Pharmaceutical HTA, specifically for end-of-life, orphan and ultra-orphan medicines.	Patient group representatives included in PACE meetings. The authors concluded that: *"information captured during PACE meetings is relevant when making decisions on EoL, orphan, and ultra-orphan medicines."*

Abbreviations: AIHTA = Austrian Institute for Health Technology Assessment; EA = early assessment; EAA = early awareness and alert; HS = horizon scanning; HTA = health technology assessment; HS = horizon scanning; N = no; NHS = National Health Service; PACE = Patient and Clinician Engagement; PCORI = Patient-Centered Outcomes Research Institute; PPIE = patient and public involvement and engagement; SMC = Scottish Medicines Consortium; Y = yes.

HORIZON SCANNING AND EARLY ADVICE FOR VACCINES

HS and early assessment in the context of vaccines are given special consideration in this section, as the evidence base for discussion in earlier sections was mainly focussed on medicines. In Australia, HS for vaccines is one of the roles of ATAGI, and so the committee and the Department may be aware of new vaccines ahead of requests from sponsors for advice. ATAGI receives technology updates via presentations by vaccine manufacturers at the annual ATAGI Industry Day, from literature reviews and decisions by regulatory authorities in other countries, and from TGA advice regarding new applications for registration. ATAGI meets six times a year and provides advice to PBAC on the evidence pertaining to new and emerging vaccines, and their effectiveness in the Australian setting.[20]

A systematic review [195] and a NICE methodology paper [280] provided the basis of discussion of HS in Europe in the following sections.

Vaccine market access in European Union countries

An article by Laigle et al (2021) provided data from a systematic review of vaccine market access (VMA) pathways from 28 countries in the European Union, plus the United Kingdom. The data was supported by further information gathered from interviews with non-industry vaccine experts from exemplar countries conducted by the authors. The experts were able to provide insight into the barriers and drivers affecting the VMA pathways and to make recommendations for improvements [195].

Information was elicited on whether HS fed into VMA pathways within each country. Fifteen countries performed HS to inform the VMA pathway. Of these, 10 performed HS once or twice yearly, and five performed HS on an ad hoc basis. The HS is usually performed by the country's Ministry of Health (MoH), or National Immunisation Technical Advisory Group (NITAG), who will initiate assessment if required [195].

There are some discrepancies between the European countries performing HS in Laigle et al's article (2021) and in the review on HS for medicines by Vogler (2022).[223] Eight countries reported to perform HS by Laigle et al, were reported as *not* having a HS system by Vogler. Vogler did however note that the same countries were members of an HS collaboration (VD, IHSI, NPF, or BeneLuxa). Laigle et al claim that their information is correct as of Q1 2020, whereas Vogler claimed that at Q2 2020, IHSI was the only active collaboration, and only two of the eight countries were part of the IHSI collaboration. Also of note, Vogler commented on the Austrian HS system as an example of cost containment as initially, Austria included only oncology medicines for HS. By

[20] ATAGI advice on vaccines: https://www.pbs.gov.au/pbs/industry/listing/procedure-guidance/6-consideration-submissions/6-5-role-of-atag-on-immunisation-request-list-vaccines accessed 28 Sep 2023

development and expansion the Austrian HS system it was later able to extend to the inclusion of COVID19 medicines and vaccines in Q1 2020, a critical time in the COVID19 pandemic.[223] It is possible that there were changes in national HS activities amongst other countries between 2019 and Q1 2020, or that the eight countries in question perform HS specifically for vaccines rather than medicines. What's more, vaccines are sometimes included under the umbrella term "medicines" in the literature and health-related websites. These discrepancies could not be resolved within the timeframe of this paper, and they serve to highlight that obtaining accurate information on current HS activities is challenging.

Early advice, according to the vaccine experts, was crucial for acceleration of VMA pathway process according to Laigle et al. Five countries used a formal process to provide early advice, and 8 countries used an informal process. Formal early advice was defined with a separate, criteria which may include documentation and timelines, whereas informal early advice tended to be given verbally and without a fee [195]. Formal and informal types of early advice were described in the article.

> *"Formal early advice…usually involves a NITAG or HTAB and is defined as a separate, established process with criteria that may include whether a vaccine is eligible for the process, documentation, timelines and, in some cases, fees.*
>
> *Informal early advice … is usually provided verbally, in face-to-face meetings, without a fee."*[195]

Table 20 provides a summary of the features of HS and early advice in the VMA pathways of the European countries included in the systematic review, and which organisation (HTA body, MoH, public health institution, or NITAG) initiates assessment of a new vaccine [195].

Table 20 Features of vaccine market access pathways in 28 European countries

Country	Horizon scanning	Early advice	Initiation of assessment
Austria		Informal	MoH
Belgium	1 or 2/year	Informal	MoH
Bulgaria			
Croatia	1 or 2/year		PH Inst
Cyprus	Ad hoc		MoH
Czech Republic			
Denmark	Ad hoc	Formal	NITAG
Estonia			NITAG
Finland	1 or 2/year		NITAG
France	1 or 2/year	Formal	
Germany	1 or 2/year		NITAG
Greece			NITAG
Hungary			NITAG
Ireland	Ad hoc	Informal	NITAG
Italy		Informal	MoH

Country	Horizon scanning	Early advice	Initiation of assessment
Latvia			NITAG
Lithuania			NITAG
Luxembourg	1 or 2/year		MoH
Malta	1 or 2/year		MoH
The Netherlands	1 or 2/year	Formal	MoH
Poland		Formal	MoH
Portugal	Ad hoc	Formal	MoH
Romania			MoH
Slovakia		Informal	
Slovenia			MoH
Spain	Ad hoc	Informal	PH Inst
Sweden	1 or 2/year	Informal	NITAG
United Kingdom	1 or 2/year	Informal	MoH

Abbreviations: MoH = ministry of health; NITAG = national immunisation technical advisory group; PH Inst = public health institution

Source: Laigle et al, 2021[195]

National Health Service (England, Wales) methods for vaccine market access

The NHS method for assessing vaccines for market access has been included as it provides the most detailed information available on the process.

According to the NICE health technology evaluation topic selection manual, prophylactic vaccinations are for consideration by the Joint Committee of Vaccination and Immunisation (JCVI), rather than through the topic selection pathway for medicines.[274] The JVCI code of practice document (revised 2013) describes that their role is:

> *"To advise UK health departments on immunisations for the prevention of infections and/or disease following due consideration of the evidence on the burden of disease, on vaccine safety and efficacy and on the impact and cost effectiveness of immunisation strategies. To consider and identify factors for the successful and effective implementation of immunisation strategies. To identify important knowledge gaps relating to immunisations or immunisation programmes where further research and/or surveillance should be considered."* [280]

Currently the JVCI advises health departments in England and Wales. The JCVI does not have a role in advising Scotland or Northern Ireland, however advice is available to them to accept if they choose. JCVI makes recommendations based on scientific and other evidence, although is not a policy maker. To assess the cost-effectiveness of vaccines, the JCVI uses NICE methodology, to assess direct health benefits for the population vaccinated, but the indirect benefits for the benefits of the program to the wider community.[280]

According to the code of practice, the JCVI's wide range of sources includes HS of emerging vaccine technologies, developing vaccines, and information on the availability of new vaccines. The IO conducts HS for prophylactic vaccines in the UK, under the umbrella of HS for medicines, therefore the JCVI is able to draw on an already available resource.[281] JCVI also receives regular reports on vaccine safety and can therefore advise on minor changes or discontinuation of current immunisation programs.[280]

A schematic of the evaluation pathway for new or existing vaccines used by the JCVI, and provided in their code of practice document, indicates that HS feeds into the first stage of the process (highlighted blue in the figure below). The evaluation pathway has been summarised in Figure by the authors of this paper.

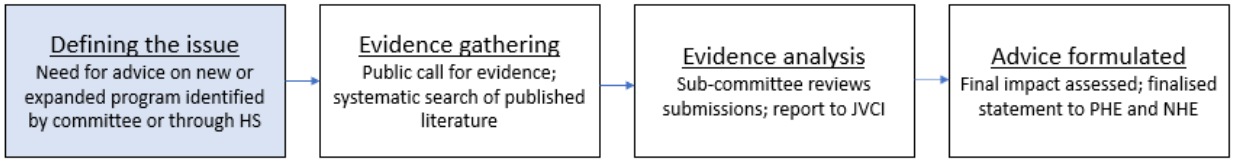

Figure 25 Schematic for the JVCI pathway for the evaluation of new and existing immunisation programs

Source: Modified from UK Government, *JCVI Code of Practice*. 2013 [280]. This work is licensed under the Open Government License (v 3.0). To view license conditions see: https://www.nationalarchives.gov.uk/doc/open-government-licence/version/3/.

IMPLICATIONS

Countries have had good intentions to conduct and collaborate in HS since the late 20th century and progress has been made. There have, however, been barriers to this progress; one of the most challenging being different goals between jurisdictions. To improve HS, Oortwjin et al suggest that the end user, the time horizon, and the scope need to be more clearly defined.[282] Earlier HS collaboration may improve the efficiency of evidence assessment.[283] Relevant stakeholders should be engaged early in the process, and smart data systems should be employed to improve efficiency.[282, 283] Focusing on areas of high unmet need and developing criteria to identify potentially disruptive technologies might have the greatest benefit.

CADTH and NICE are leading the way in having HS integrated into regular HTA activity and they have clear processes that could be applied to the Australian setting, should a stand-alone HS activity for medicines be (re-)introduced to Australia.

Another possibility is the Office of HTA, in the Australian Government Department of Health and Ageing, forming an HS collaboration with NICE/NIHR-IO and CADTH. There is a track record of working with these countries when the EuroScan HS network existed and there is a new collaboration between these three agencies in HTA. According to PBS News the priority areas of this AUSCANZUK collaborative venture include: the future-proofing of HTA systems, work-sharing and efficiency gains, and sharing of information

on digital and artificial intelligence developments[21]. Whilst efficiencies could be realised via an HS collaboration, there are also risks associated with it, key of which is the value of the investment. The lack of evidence on the effectiveness and cost-effectiveness of HS makes this question hard to answer. To be on an equal footing in such a collaboration on HS, Australia would need to establish its own automated intelligence gathering methods, for identifying local information at the least. Sharing the intelligence gathering (or filtration) would reduce duplication and potentially produce efficiencies in the subsequent HTA, particularly if there is also HTA work-sharing between these three organisations.

A small number of studies were identified that assessed individual HS systems by evaluating the proportion of medicines that ended up undergoing full HTA following identification and filtration. Diagnostic accuracy measures of sensitivity and specificity were commonly employed to express the "success" of the HS system. For example, one study assessed outputs of the University of Birmingham National Horizon Scanning Centre (NHSC)[22] for NICE between 1999 and 2010. [284] This study found a positive predictive value of 0.39 for HS topics identified that were eventually referred to NICE for appraisal, with a false positive rate of 60%. Of 291 NICE appraisals of medicines listed on the NICE website to December 2010, 44 did not have a corresponding HS report. Considering that 23 of these would not have fit the criteria for HS at the time, it was estimated that NHSC sensitivity at identifying relevant medicines over 10 years was 0.92 (95% CI 0.89, 0.95). However, the true measure of the success of an HS system is the impact of the intelligence on planning and preparation within the health system, and none of the identified studies evaluated this. Changes in planning because of HS are much more difficult to assess, and hence HS systems have not been properly evaluated for this outcome.

Should HS be undertaken in Australia, several key points would need to be considered. Firstly, the purpose of the HS should be clearly defined as this underpins the perspective of HS. For example, if the purpose of HS is to enable planning for the funding of high-cost medicines, this will influence the selection and prioritisation of topics. A broader HS system may consider all technologies that are potentially disruptive and likely to have an impact on the way healthcare is delivered. The primary purpose of the systems included in this review was health service planning, and if Australia was also to use HS for this purpose, then it would make sense for it to be undertaken within government/s, or by agencies contracted by government/s (as it was when HealthPACT was responsible for HS in Australia). Whether there is capacity within federal and/or state and territory government or HTA agencies would need to be explored. Such an activity would also

[21] PBS News Last update 5 Sept 2022 https://www.pbs.gov.au/info/news/2022/09/collaboration-arrangement-between-the-department-of-health-and-aged-care

[22] The National Horizon Scanning Centre's horizon scanning activity moved to the University of Newcastle's Innovation Observatory in 2017.

benefit from working in partnership with industry and patients who are often aware of emerging therapies well before these are reported in the literature. There may be ancillary benefits in terms of greater efficiency of the HTA if the HS process for the technology was performed or coordinated by the same organisation. The method for HS would also need to be considered; whether it is proactive (such as ongoing surveillance of particular topics) or if it is reactive (topics submitted by various sources including stakeholders). Obviously, resource constraints will influence this decision and international collaboration may provide a partial solution. It should be noted that Australia currently has an HTA evaluation process that can be undertaken in parallel with the regulator (TGA) and so medicines and vaccines are identified prior to market entry anyway. This is, however, typically not the case for highly specialised technologies (cell and gene therapies) and medical devices.

ESA and EVP are processes that offer benefits primarily to industry. EVP is of limited value to HTA because of the associated uncertainty with assessments conducted so early in the technology lifecycle. As with other types of early assessment, there are meaningful opportunities for stakeholders, particularly patients, to influence the development of the technology by identifying priorities for improvement in treatment and allowing a greater understanding of the lived experience of the condition.

ESA is undertaken by many regulatory and HTA agencies and is increasingly done in tandem and collaboratively across jurisdictions. Most HTA agencies do not evaluate technologies that they have provided scientific advice on, and so efficiencies in the HTA are unlikely to be realised, except perhaps through possible improvements in the quality of trial evidence submitted. The services provided by HTA agencies and regulators are done on a fee-for-service basis, so there is some monetary return, but it is difficult to see if any other system-wide benefits accrue.

On the other hand, patient recommendations in early product development, if taken on board, could help to focus on the patient priorities for disease management and enable better value propositions of the medicine for industry and potentially benefit patients. In the ESA process, patient engagement before the design of pivotal trials could ensure patient-relevant outcomes are measured and trial design is acceptable to patients. Benefits to the wider health system are unquantified and without systematic approaches to the use of early assessment, where an overall increase in the appropriate targeting of product development can be observed, these benefits are likely to remain hypothetical. Opportunities to influence product development and input into trial design are likely to be limited in Australia due its small market and with the bulk of the research occurring overseas. ESA might be better targeted to the triallists themselves, perhaps through discussions with organisations like the Australian Clinical Trials Alliance, and address both Australian trials and international multi-centre trials where Australia is a site.

With regard to EVA, as proposed by NICE, there does not seem to be an equivalent in Australia. The focus on technologies that address high unmet clinical need, in the

context of system wide priorities, is a key factor in EVA. A major difference that could make this approach difficult in Australia is the fragmentation of the health system across federal and state governments. Whilst in the UK, NICE can consider technologies for health systems that may be implemented across the NHS, Australia does not really have a mechanism for the evaluation and implementation of interventions across the whole health system. Other technologies considered by the EVA, such as digital aids for therapy, could potentially be considered through the MSAC. As previously mentioned, NICE EVA is for digital technologies, devices and diagnostics. It is unclear if this type of approach would work for the majority of medicines and vaccines, with the exception perhaps for rare diseases and highly specialised technologies. The criteria used for the NICE EVA include unmet clinical or social need in priority health areas. One example of a medicine that was not for a rare disease and that might have qualified in Australia for EVA was the direct-acting antivirals for hepatitis C. The definition of unmet need is contentious here and would need to be clearly defined if a similar process was initiated in Australia.

Whilst it is too early to conclude if EVA, as implemented by NICE, is an effective way to address health system priorities and enable earlier access to effective technologies, CED in some form is likely to be beneficial if applied to high priority disease areas where there is unmet clinical need, where a technology shows promise but there is limited evidence available demonstrating that, and where the magnitude of clinical benefit and cost-effectiveness are uncertain. A clear definition of unmet clinical need and a prioritisation process that targets medicines in high priority disease areas would be crucial to the success of any such program. Additionally, there should be clear expectations around the development of evidence to confirm (or not) the promise of the medicine, with policy makers, academics, economists, clinicians, patients and HTA evaluators to advise on how data should be collected and interpreted. Where confirmatory trials are pending, funded access should not be implemented immediately if the trial recruitment will be affected. There should also be consequences if expectations around evidence development or potential benefit are not met, such as clawback provisions on price and managed exit criteria. A patient consenting process would need to be considered (likely at the level of the treating clinician), noting safety and effectiveness of the medicine at funded access would be uncertain and that there is always the possibility that the medicine could be subsequently withdrawn. More discussion about CED programs can be found in Papers 4c, 8 and 9 of the HTA Review.

It should be noted that Australia has a medicines access program for rare diseases (the Life Saving Drugs Program) and there are other ways to access drugs that are not registered in Australia (TGA's Special Access Scheme and Authorised Prescribers) and some medicines can be accessed through clinical trials or compassionate access schemes. Early access to medicines schemes (such as NICE's EAMS or South Korea's CAED) are other models concerning funded access that are specific to medicines rather than other technologies. It is worth considering the topic selection and prioritisation

process, and the wide stakeholder engagement, used in EVA should some form of early HTA or coverage with evidence development be introduced in Australia.

Advice from the Reference Committee[23] in response to the findings of this paper highlighted that there are no existing mechanisms or methods to collate patient perspectives formally and routinely in Australia. This would need to be addressed if patient perspectives were to inform HS and EVA programs in Australia. If Australia were to undertake HS and EVA, PARADIGM (Patients Active in Research and Dialogues for an Improved Generation of Medicines)[24] provides an online toolkit[19], which has been specifically developed for patient engagement in early dialogue (usually prior to Phase 3 clinical trials) based on the experiences of CADTH, NICE and EUnetHTA. This includes detailed guidance for patient interviews and patient attendance at meetings with industry and HTA body representatives. PARADIGM is an international collaboration, funded by the Innovative Medicines Initiative with support from the European Federation of Pharmaceutical Industries and Associations. The methods undertaken by PARADIGM may provide a potential starting point if patient perspectives in medicine development were to be considered for routine collation to feed into ESA within Australia. Advice from the Reference Committee[23] also points to CADTH as a leading resource for patient engagement in the ESA process.[25]

Overall, a key limitation of all the evidence for HS is the lack of information on its effectiveness and impact on the health system in terms of preparedness and planning. Despite being established for many years, the impact of HS, and any changes that have been made to health services in light of what has been discovered, remain unexplored. There is potential for HS to be of benefit if it identifies disruptive technologies at an early stage, particularly highly specialised technologies that impact on the public hospital system, and this results in changes to health system preparedness. Collaboration on HS for emerging technologies is a way to maximise efficiency from the resource use associated with HS and may allay some of the risks associated with the investment in this activity. Engaging patient and carers in HS is mentioned by HS agencies, with these stakeholders able to suggest topics for consideration in many cases. However, there was limited evidence that patients are a regular or targeted source of information for HS systems.

Horizon scanning and early assessment may have a role to play in preparing the evidence and the health system for new medicines, vaccines and highly specialised technologies. However, the precise purpose, timing and scope of these activities would

[23] Reference Committee feedback on first draft of this report, received 11 August 2023.
[24] Information available online: https://imi-paradigm.eu/ (Accessed 23 August 2023).
[25] Information available online: https://www.cadth.ca/patient-involvement-scientific-advice (Accessed 23 August 2023).

need to be carefully thought through, along with the potential for creating efficiencies in the HTA process.

Paper 3: HTA Methods: Determination of Population, Intervention, Comparator, and Outcome (PICO)

Health Technology Assessment Policy and Methods Review Papers

March 2024

make history.

HTA Methods: Determination of Population, Intervention, Comparator, and Outcome (PICO)

Paper 3 in Health Technology Assessment Policy and Methods Review Papers

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Acknowledgements

We would like to thank the following people who took the time to provide assistance and/or fact checked the information included in this paper –

Ms Lydia Loke, Lead Specialist, Drug and Vaccine Evaluation, Agency for Care Effectiveness (ACE), Singapore Ministry of Health, Singapore

Dr Alric Ruether, Head of International Affairs, and Irene Urbina of the Institute for Quality and Efficiency in Health Care (IQWiG), Germany

The Department of Health and Aged Care project staff who coordinated the HTA Review and worked with AHTA on delivering each of the papers.

The HTA Policy and Methods Review Reference Committee for feedback and guidance throughout the project.

SCOPE OF RESEARCH

The research topics for Paper 3 are outlined in Research Topic section and summarised below. The key focus of Paper 3 related to the development of the population, intervention, comparator and outcomes (PICO) framework used in HTA, particularly determining the comparator and the outcomes of interest.

The objective of Paper 3 was to compare the Australian policies and processes used to develop a PICO, and included how stakeholders were involved, and whether and how equity considerations were incorporated. Areas of special interest that were to be covered by Paper 3 included technologies: for rare diseases; for populations with high unmet clinical need; for disadvantaged populations; that are accompanied by uncertainty in long-term outcomes; and, that are codependent. The Paper also considered recent reforms to the PICO process.

SUMMARY OF FINDINGS

Across the key jurisdictions of interest, there were two main approaches to developing the PICO criteria. The first approach involves a scoping phase, where input from stakeholders is incorporated to ensure that the research question to be addressed is relevant to the needs of decision makers and reflect what is important to other stakeholders (clinicians, patients, and their carers). This approach is used in Australia by the Medical Services Advisory Committee (MSAC) and the Australian Technical Advisory Group on Immunisation (ATAGI). It is also used internationally by the National Institute for Health and Care Excellence (NICE) in England, the European network for Health Technology Assessment (EUnetHTA), and the Institute for Clinical and Economic Review (ICER) in the USA.

The second approach is for there to be no separate scoping phase, but to rely on the sponsor/applicant of medicines/vaccines/highly specialised technologies to follow guidance on how to develop the PICO criteria, and for this information to be included in their submission at the time of applying for reimbursement.

In defining the target Population/indications for new technologies, those jurisdictions with reimbursement occurring prior to HTA (i.e., with coverage granted at market access) require the population to be identical to the registered indication (occurring in Germany, and in special cases in the Netherlands and France). All the other jurisdictions assessed - which reimburse after HTA - allow the reimbursed population to be narrower than the registered indication, although trial evidence for the whole population (as well as subgroups) is still requested. Australia, England, France and the USA request that the assessment consider inequity between patient subgroups, and whether the proposed new treatment will reduce or increase inequities. NICE are considering incorporating distributional cost-effectiveness frameworks, which stratifies subgroups based on equity, which may be defined as part of the Population.

In defining the Comparator, every key jurisdiction suggested that it should be based on current clinical practice. This may or may not be a registered treatment, as access may be available through special access schemes, or used off-label. Australia also requests that near market comparators are included if relevant. Slight differences were found on whether standard practice should be based on what is most frequently done, or on what is recommended in clinical practice guidelines (irrespective of local access to the technology). Multiple comparators were allowed across all jurisdictions if there were target population subgroups for whom different treatments would be commonly used. In Australia, the PBAC must also be mindful that it is not permitted to recommend a medicine that is more costly than alternative therapies for the same indication, without that medicine returning greater benefits in some way. In practice this means that alternative therapies that are not the main comparator may be relevant to consider for the purposes of pricing. Internationally, as in Australia, price negotiations often occur as a separate step to the HTA, and many jurisdictions use international reference pricing (of the same medicine) rather than using the comparator as a reference for pricing.

The most important Outcomes for all jurisdictions were stated to be mortality, morbidity, and quality of life. There was also consistency that surrogate outcomes

may be used, if appropriately validated. Appendix 5 of the current *PBAC Guidelines* describes how surrogate outcomes should be properly validated [285]. However, internationally, exceptions are allowed if the condition is a rare disease, particularly if the treatment is an emerging technology, such as a cell or gene therapy. Guidelines for the Australian Life Saving Drugs Program suggest that, in these instances, there must at least be biological plausibility linking the surrogate with final outcomes. Some jurisdictions use patient-reported outcome measures (PROMs) as a means of demonstrating impact in the absence of direct health benefits. Health Improvement Scotland (HIS) emphasises that PROMs should be collected in the assessment of ultra-orphan medicines, for this reason.

For prophylactic vaccines, a broader perspective is required to account for benefits beyond the individuals vaccinated, such as reduced transmission and other possible effects such as herd immunity, age-shifting of diseases, and cross-protection against other diseases. These are recognised by most HTA agencies and payers (including in Australia).

Varying levels of guidance were available regarding non-health outcomes, and on whether and how to incorporate the impact of the proposed treatment on those people who are associated with the person receiving the treatment. For ultra-rare conditions (fewer than 10,000 people in the USA), ICER gives greater weight to the intervention's impact on patient and carer productivity, education, disability, and other societal considerations. In Australia, the PBAC and MSAC state that carer health outcomes (including quality of life) may be incorporated into sensitivity analyses in a submission or application for funding, while in England, NICE states that economic evaluations should incorporate both patient and carer outcomes. Most jurisdictions did not provide guidance on how carer outcomes should be incorporated into HTA reports and assessments. In Canada, new guidelines on preparing vaccine assessments recommend inclusion of outcomes such as productivity, education, and that the environment should be considered.

Reforms to HTA processes over recent years have seen a willingness to accept more uncertainty about the effectiveness of promising new therapies at the time of reimbursement, with collection of real-world (observational) evidence after reimbursement. Patients with severe disease and high unmet clinical need may therefore access treatments earlier. Different agencies have introduced processes to improve the collection of real-world data when trial data are insufficient for decision making. Any PICO criteria that are developed could therefore influence what outcomes are studied in primary data collection.

At the same time as there is an increasing emphasis on allowing access to innovative treatments faster, there is also a shift to incorporating more public and patient views into the HTA process. If this is to be achieved for the process of developing the PICO criteria, the best way would be through the separate scoping phase (in systems that provide it), where the draft PICO criteria can be consulted on by the public and patients. A limitation of this approach is that it could increase the length of the overall medicine assessment process. This would conflict with the aim of reducing the time to reimbursement but might still be informative regarding how patient-relevant the proposed outcomes are, and whether there are subgroups of the proposed population, for whom the comparator would be different than that proposed. It would also contribute to the goals of relevance, equity and fairness in the HTA process [286]. There might be gains in timeliness as the approach could feasibly reduce the number of resubmissions arising from the

initial submission not fully capturing the appropriate population subgroups and comparators. There is evidence from NICE that patient input can have an influence on the scope, for example, in an assessment of a treatment of multiple sclerosis, patient group input identified patient sub-groups and appropriate comparators [287]. It is, however, acknowledged that this 'added value' might only affect a small number of submissions. In Australia, the time allowed for developing the PICO criteria for an MSAC application (after triaging/suitability assessment and before lodgement of the assessment report) is four months [288].

For innovative technologies that are likely to have a substantial impact on the healthcare system, consultation on the organisational impacts is warranted. This could either sit alongside the regular HTA process or be undertaken in the separate scoping phase.

IMPLICATIONS

Australia has agreed to collaborate with the UK, New Zealand and Canada, to explore the feasibility of recognising or using each other's HTA information and explore running a pilot for joint clinical assessment (JCA)[26]. In the assessment of new medicines, the key difference between these jurisdictions for the development of the PICO criteria, is that NICE has a separate scoping phase, allowing clinicians, patients and public to comment on the PICO. In Australia this occurs for the test component of codependent technologies, and for highly specialised technologies assessed by the MSAC, but not for medicines assessed by PBAC. Internationally, the collaborating agencies other than NICE (i.e. Pharmac, CADTH, Institut national d'excellence en sante et an services sociaux (INESSS), Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG)) do not have a scoping phase involved in the generation of PICO for medicines[27]. An alignment of process and of the national-level PICO underpinning specific technologies being proposed for reimbursement, will be required before JCAs can occur. This is being realised in the pilot JCAs being undertaken through the European Union HTA Regulation, where submissions are required to address multiple national-level PICOs in a single dossier being submitted for HTA evaluation and appraisal. Of the listed collaborating agencies, only PBAC and Pharmac currently evaluate vaccines. Vaccines considered by the PBAC have an additional step, with advice provided by ATAGI. Pharmac have recently undergone a review and have stated that future work will include securing input from a more diverse range of stakeholders earlier in their assessment and decision making. This could possibly occur at the PICO development stage.

Even apart from the goal of working together with other jurisdictions on JCAs, Australia could consider introducing a scoping phase and PICO ratification process for medicines and highly specialised technologies that are appraised by PBAC. To ensure, however, that this does not unnecessarily congest the HTA evaluation and

[26] https://pharmac.govt.nz/news-and-resources/news/2023-07-20-media-release-pharmac-joins-international-collaboration-to-advance-use-of-health-technology-assessments/

[27] Although some of the non-medicine bodies such as Health Technology Wales and Scottish Health Technology Group do have a form of scoping

appraisal process, it should perhaps be reserved for medicines and highly specialised technologies that are deemed most likely to be disruptive to the health system.

Australia already has a process in place for reviewing classes of medicines once they have been established in clinical practice (PBS Post-market reviews) and that process is able to consider sequencing of treatments and thus whether the initial PICO should change after the medicine has been used widely and how the availability of new treatments available on the market may affect the population and comparator. Although this occurs after the initial submissions and funding of medicines, the process may influence new submissions to PBAC for alternative medicines or for the same medicine but for an extended patient population (flow on changes).

Consideration could be given to whether the PICO criteria (traditionally used to define the research questions for the clinical evaluation of safety and effectiveness) should also define elements relevant to the economic and financial impact analyses, as well as the alternative technologies relevant for pricing.

Overall, the current policies and processes for developing the PICO criteria that guide HTAs in Australia are generally satisfactory for most health technologies evaluated but could be improved by introducing a PICO ratification process for PBAC assessment of first in class medicines and highly specialised technologies that are potentially disruptive. During the scoping phase, stakeholders such as patients, clinicians, State and Territory governments, industry and the Australian Government Department of Health and Aged Care ('the Department') could provide valuable input for defining the population (or subgroups) of interest, outlining current practice and health service delivery, and health outcomes considered relevant to patients and to decision makers. Well-defined PICO criteria for certain select medicines and technologies may improve the quality of an initial submission, reduce the requirement for a resubmission, and thus expedite and align reimbursement decision making. Work-sharing and collaboration with other countries would be facilitated by the development of a specific PICO pre-assessment process for certain medicines and by amending some areas of the Australian HTA guidance documents.

LITERATURE SEARCH RESULTS

The process of selecting relevant documents from grey literature (reports, guidelines and webpages of HTA agencies and governments) and peer-reviewed journal articles for this scoping review is given in the PRISMA-ScR flowchart (Figure 36).

Searches identified 21 relevant peer-reviewed articles, and an additional 8 articles were derived from citation chasing. Further relevant documents were identified from grey literature (searches of HTA agency and government websites) and targeted searches for variations in methods relating to developing the PICO criteria for vaccines, cell and gene therapies, and treatments for rare diseases.

The documentation for many non-English speaking countries was not available in English, therefore, where possible, information was extracted from peer-reviewed journal articles.

No literature was identified specifically referring to the benefits/risks of different approaches to developing the PICO criteria. This has been considered instead in the Implications section.

ASSESSMENT OF MEDICINES

The evaluation of medicines frequently involves a different process or set of guidance than the assessment of vaccines. The results have therefore been separated into medicines and preventative vaccines. The pathway that therapeutic vaccines for affected individuals (e.g. monoclonal antibodies) are evaluated is usually as per the process for medicines.

Although the Medical Services Advisory Committee (MSAC) are not involved in the assessment of medicines, they are mentioned the findings of this paper due to their involvement in the assessment of tests for codependent technologies.

POLICIES AND PROCESSES FOR DETERMINING THE PICO

With respect to the process of developing the PICO, the following were considered:

- Is there a separate process for determining the PICO?
- Is there any mandatory pre-submission advice/consultation about the PICO?
- Is the PICO developed by the applicant/sponsor?

Table 21 Policies and processes for developing the PICO for medicines

Country	Organisation	Separate process	Pre-submission advice	Developed by applicant/sponsor
Australia	PBAC	●	●	●
Australia	MSAC	●	●	◑
England	NICE	●	●	●
Wales	AWMSG	●	○	●
Scotland	SMC	●	●	●
Europe	EMA and EUnetHTA	●	●	◑
France	HAS	●	●	●
Germany	IQWiG	●	●	●
The Netherlands	ZIN	●	●	●
United States	ICER	●	●	●
Canada	CADTH	●	●	●
Canada (Quebec)	INESSS	●	●	●
South Korea	HIRA	●	●	●
Taiwan	CDE/NIHTA	○	○	●

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Two main *approaches* for developing the policy/research questions and specifying the associated PICO criteria were identified in the key jurisdictions considered for Paper 3:

1. an *approach* that uses a separate scoping phase to determine the assessment framework. This involves developing the appropriate the research questions and defining the corresponding PICO criteria prior to the clinical and economic evidence being obtained for assessment.
2. an *approach* without a separate scoping phase where the market authorisation holder/submission sponsor defines the scope of the assessment framework by specifying the research questions and consequently the PICO criteria. This is achieved by following formal guidelines of the relevant HTA agency and with or without additional pre-submission advice from the HTA agency.

Australia currently uses both approaches depending upon the type of technology being assessed [285, 289, 290]. A description of the processes in Australia is provided below, followed by summaries for jurisdictions that do and do not use the separate scoping phase for determining the PICO.

Australia

In Australia, sponsors of submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) for listing of medicines through the Pharmaceutical Benefits Scheme (PBS) should follow advice provided in the *PBAC Guidelines* regarding the construction and content of the submission. The Guidelines provides information on how to prepare evidence of the comparative safety, effectiveness and cost-effectiveness of medicines, as well as fixed-dose combination products, vaccines, codependent technologies, and nutritional products [285]. For Category 1 and Category 2 submissions[28], the PBAC submission and assessment of the submission can be carried out in parallel with the market authorisation process administered by the regulator, the Therapeutic Goods Administration (TGA) [291].

The submission to the PBAC is usually prepared by the medicines' sponsor. Section 1 (Context) of the submission includes the clinical claim for the medicine (in terms of comparative safety and effectiveness) and the PICO criteria upon which this claim is based. This includes outlining the target Population, describing the characteristics of the disease in the Australian population, clearly outlining any subgroups and the patient characteristics for the subgroups. For the Intervention, sponsors are requested to describe the pharmacological action, line of therapy, clinical setting and co-administered therapies, and to state whether the indications are consistent with the (draft) Product Information submitted to the TGA. For the Comparator, the submission should include the nominated main comparator and arguments to support the choice of this. In Section 1, sponsors are requested to outline the critical patient-relevant outcomes addressed by the submission.

A pre-submission meeting between the sponsor and the Department of Health and Aged Care (the Department) is not mandatory but is available if considered to add value to the submission e.g., advice on selection of the appropriate comparator for the PICO. For medicines, there is no formal PICO confirmation (ratification) process for the PICO criteria to be used in the submission [285]. During the assessment process, there are some

[28] Category 1 submissions involve a request for PBS or NIP (National Immunisation Program) listing of one or more of the following: a first in class medicine or vaccine, and/or a medicine or vaccine for a new population, or a drug with a codependent technology that requires an integrated submission to the PBAC and MSAC or a drug or vaccine with a TGA provisional determination related to the proposed population.

Category 2 submissions relate to a request for PBS or NIP listing of a new medicine or new vaccine, a new indication of a currently listed medicine or vaccine, or to make material changes to a currently listed indication and that do not meet the criteria for a Category 1 submission.

opportunities for the applicants to respond, if required, to any potential comments on the PICO criteria in the commentary on the submission (e.g. via the Pre-subcommittee response [PSCR] or Pre-PBAC response) prior to PBAC consideration of the medicine for PBS listing. This is also the case for medicines considered by the PBAC prior to subsequent inclusion in The Life Saving Drugs Program (LSDP) for the treatment of rare[29] and life-threatening diseases (i.e. the process up until consideration by PBAC is identical for medicines that are ultimately considered for PBS or LSDP funding) [292].

The PICO criteria may change in a resubmission in response to concerns raised by PBAC to the previous submission (e.g., change to population or comparator).

For medicines undergoing a parallel assessment process by the TGA and PBAC, the PBAC outcomes for items that are recommended or deferred are not published until a positive TGA delegate's overview has been received, and the Public Summary Document will not be published until the medicine is registered for that indication by the TGA. If the indication approved by the TGA is different to the indication proposed by the sponsor, this could impact the PICO criteria subsequently considered by PBAC for the proposed PBS listing. Amendment to the PICO and additional information may be requested of the sponsor by the PBAC.

Technologies are codependent when one technology relies on another technology to achieve its intended purpose or enhance its effect. To date, most codependent technologies assessed in Australia have been medicine and test combinations, where the new medicine is submitted for listing on the PBS and a related companion diagnostic test is required to refine patient selection and eligibility for the new medicine. Consequently, the companion diagnostic test is simultaneously considered by the Medical Services Advisory Committee (MSAC) for listing on the MBS [290]. Applications going to the MSAC have a separate process for determining the PICO criteria. Sponsors are required to put in an application outlining the proposed claim, PICO criteria, and clinical management algorithms for both the test and medicine components, although the MSAC's focus is the testing component and issues of co-dependency. The standard process is then for an HTA group to develop a PICO Confirmation to be considered by the PICO assessment sub-committee (PASC) of the MSAC. If the PICO criteria are straight forward in the codependent application, the Department and the MSAC executive may permit the sponsor to bypass the PASC process and progress straight to the development of a codependent submission. If not, the proposed PICO Confirmation is considered by PASC and may also be put forward for public consultation and/or targeted consultation with key stakeholders [290]. Although the PICO Confirmation considered by PASC includes PICO criteria for both the companion test and the medicine, the advice from the committee is focused on the PICO criteria relevant to the codependent test when ratifying the PICO.

[29] Defined as fewer than 1 in 50,000 in the Australian population

The assessment pathway selected for highly specialised technologies (HST) is guided by the 2020-25 National Health Reform Agreement (NHRA) [293]. Where the HST is likely to be delivered in a public facility, the MSAC and PBAC Chairs, together with representatives from the States and Territories, jointly decide on whether the MSAC or PBAC should assess the application for a new medicine or therapy. If the therapy meets the high cost, highly specialised criteria as outlined in the 2020-25 Addendum of the NHRA, and does not fall within the remit of PBAC as set out in the *National Health Act 1953*, it will be considered by the MSAC. MSAC's role is to provide recommendations on technologies other than medicines eligible for listing on the PBS, which includes HSTs delivered as state-based services [290]. For example, onasemnogene abeparvovec, a gene therapy for spinal muscular atrophy, was considered by PBAC, whereas gene therapies voretigene veparvovec and etranacogene dezaparvovec and CAR-Ts have been, or will be, assessed by MSAC. This has implications for determination of the PICO criteria as MSAC submissions benefit from ratification of the PICO by PASC prior to development of the submission. The PICO Confirmation process does, however, increase the overall period of assessment by around 4 months (the time between suitability assessment and the lodgement deadline for the Applicant Developed Assessment Report (ADAR)). However, the intent is for applicants to engage in the MSAC pre-assessment process prior to the time they are intending to submit their ADAR for consideration by the MSAC, given the MSAC pre-assessment and assessment phases are separate processes.

Key jurisdictions with a separate approach to developing the PICO

Whereas Australia has *partial* use of a scoping phase to inform the development of the PICO, NICE in England, ICER in the United States of America (USA), and projects done in Europe as under EUnetHTA 21 Joint Clinical Assessments (JCA) all have *full* implementation of this approach. Once the PICO are determined, in England and Europe the collation of the evidence dossier is then performed by the sponsors, whereas in the USA, ICER drafts the evidence report.

England

The NICE Technology Appraisal and Highly Specialised Technologies Programmes are used for assessing new technologies (typically, new medicines or new licensed indications) and enables NICE to produce both reimbursement decisions and clinical practice guidance after the technology receives market authorisation in the UK. The single technology appraisal process is used for the first assessment of a medicine and to update existing guidance. It is the most used process.

NICE is required to select topics that reflect national priorities for health and care. However, this includes all medicines that are new to the UK market or have a significant new therapeutic indication. This includes therapeutic vaccines. Medicines which are expected to get appropriate regulatory approval within 24 months are eligible. For other topics, NICE engages with stakeholders to identify priorities of the health

system[274]. Many academic and non-academic institutions are involved in informing NICE regarding new and emerging technologies and topic selection. After identifying topics through the topic selection process, NICE develops a draft scope for each potential evaluation and seeks the views of stakeholders. The first step in the scoping process is to identify information about the technology or technologies. This is done using literature searches, checking the availability of relevant evidence, and requesting information from the sponsor. NICE uses this information, along with the technology briefing, to prepare a draft scope. For new technology appraisals and highly specialised technologies guidance, scoping normally takes place during (and is used in) topic selection.

The aim of the NICE scoping process is to define the research question, develop a framework for the assessment, and define the PICO criteria [27]. Issues considered during development of the scope includes elements of the PICO (the population(s) for whom the technology is being evaluated including any relevant subgroups; the technology being evaluated; the relevant potential comparator technologies; the principal outcome measures appropriate for the analysis). After consultation with a wide range of stakeholders, the final scope is used to confirm that the topic is suitable for evaluation and the scope is available for use during the evaluation.

In Wales, the HTA appraisal of new medicines is performed by the All-Wales Medicines Strategy Group (AWMSG). NICE recommendations are applicable to both England and Wales so NHS Wales can access a medicine if recommended by NICE. Where NICE carries out an HTA appraisal of a medicine which has already been appraised by AWMSG, NICE guidance can replace advice from AWMSG. AWMSG uses the NICE guidelines and criteria to assess the clinical and cost-effectiveness of medicines. AWMSG topic selection is influenced by the appraisals planned by NICE as AWMSG does not usually perform HTA of medicines where NICE has published guidance within 12 months of market authorisation.

In Northern Ireland, the HSC is legally required to provide access to medicines recommended by NICE.

Europe (as a single jurisdiction)

In preparation of the implementation of joint scientific consultations under Article 16 of the HTA regulation (EU 2021/2282), the EMA and HTA bodies (HTAbs) are offering interim advice referred to as Parallel EMA/HTA body (HTAb) Scientific Advice from September 2023 to January 2025 [294]. This scientific advice can be provided at any stage of a medicine's development, I.e., before authorisation (when developing trials), or in the post-authorisation phase (prior to reimbursement). As an outcome of the parallel EMA-HTAb Scientific Advice procedure, the applicant will receive the EMA Scientific Advice Letter and individual Written Recommendations (non-consolidated) separately by each of the participating national HTAbs. This process promotes optimal and robust evidence generation for both the regulators and HTAbs. This advice can include

elements of the PICO, such as whether the patients to be included in a study are sufficiently representative of the population for whom the medicine is intended for use; the appropriate outcomes to measure in the studies; and whether the medicine is being compared with an appropriate comparator.

In addition to this advice, Europe is developing a centralised submission/evaluation process for certain types of medicines (new drugs for cancer, neurodegenerative diseases, diabetes, HIV, viral diseases in general, autoimmune diseases, other immune deficiencies, and rare diseases). Under the EUnetHTA 2021 framework, for Joint Clinical Assessments, developing the PICO occurred during the scoping process [295, 296]. Sponsors were asked to provide their proposed PICO for assessment. The Joint Clinical Assessment (JCA) secretariat then surveyed EU member states to collect information on their needs. If different member states had different needs (such as different comparators), there may be multiple sets of PICOs. A face-to-face scoping meeting with the sponsors allowed discussion regarding the PICO criteria, and the need to adapt to the challenges of specific technologies [297]. Once the scope was finalised, it was provided to the sponsor, and enabled them to submit an evidence dossier for evaluation that met the needs of the EU member states.

United States of America (USA)

In the USA, medicine provision and pricing are done through a mix of private and government plans, with pricing decisions being influenced by insurers, manufacturers, wholesalers, pharmacies, and pharmaceutical benefit managers. Although there is currently no governmental HTA body in the USA, the Institute for Clinical and Economic Review (ICER) provides a similar function [298]. ICER select topics to assess and have a separate process for establishing the scope and seeking feedback from patients, clinical experts, medicine manufacturers (for the intervention to be assessed and the comparator) and insurers on the scope, prior to initiating the assessment [299].

Key jurisdictions without a separate approach to developing the PICO

Like the process in Australia for medicine submissions to PBAC, sponsors of medicines in Canada, France, Germany, the Netherlands (for out-patient medicines), Wales and Scotland submit their dossiers without a separate process to determine the PICO criteria. Although these jurisdictions do not mandate pre-submission advice, this is often available at the national level on request.

European countries

In the Netherlands, sponsors of medicines may request advice from the Health Care Board (College voor zorgverzekeringen; CVZ) on the appropriate comparator and, outcomes and to discuss the methodology of the pharmacoeconomic analysis. There are two different pathways allowing medicines to be included in the basic health care package (either full inclusion if the safety and effectiveness can be established or

conditional inclusion for orphan medicines for treatment for severe disorders with an unmet clinical need, where further research into the effectiveness is still required) [300]. In both of these scenarios, no separate scoping phase prior to the assessment occurs.

In France, early dialogue is optional between Haute Autorité de Santé (HAS) and pharmaceutical companies. The purpose is to provide sponsors with advice during the developmental stage (when pivotal studies are being planned), so that good quality evidence is generated to inform an HTA [257]. Sponsors may ask questions about the trial population and its generalisability with respect to the claimed indication, the clinical trial comparator and/or other clinically relevant comparator(s), and the primary and secondary outcomes (including patient-reported outcomes) [257]. This early advice would then inform the submission for reimbursement, without a separate scoping phase. For innovative medicines, the advice can be provided in a face-to-face meeting, or as an accelerated procedure without a face-to-face meeting [101].

In Germany, there is also an emphasis on the Federal Joint Committee (G-BA) providing optional "early" advice, during the planning of studies, such as the relevant comparator for the German setting. Once a sponsor wants to market a new medicine, they need to undergo marketing authorisation by the EMA. Following marketing authorisation, patients can have funded access to all medicines (excluding over-the-counter medicines and lifestyle medicines) entering the market. Within three months, the company must submit a dossier demonstrating comparative safety and effectiveness versus the appropriate comparator treatment. The dossier is then forwarded to the Institute for Quality and Efficiency in Health Care (IQWiG) for a detailed comparison of the new medicine against the comparator. No separate scoping phase is performed prior to the dossier being submitted. Companies may request advice from G-BA on the appropriate comparator(s) and studies to be submitted[301]. For orphan medicines, an abbreviated dossier is required by the G-BA. Early benefit assessments are not required for new formulations of an existing drug, biosimilars, or reserve antibiotics (those effective against multi-resistant bacterial pathogens, where there are limited alternative therapies).

Scotland

An independent HTA agency, the Scottish Medicine Consortium (SMC) provides recommendations to NHS Scotland on the clinical and cost-effectiveness of medicines newly authorised from the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA), new formulations and the new indications for medicines which have already been assessed by SMC. The SMC only assess prescription medicines; they do not assess vaccines, generics, biosimilars, pharmacy and general sales list medicines, blood products, and diagnostics.

SMC carries out HTA appraisal as a response to a submission by a company/sponsor holding market authorisation. The submission to the SMC is prepared by the applicant or sponsor. While the term PICO is not included in the submission guidance for New

Product assessments [302], guidance on completion of the submission form includes selecting the relevant population, comparator(s) and outcomes [302]. Submissions where a companion diagnostic test (codependent test) is required to identify patients eligible for treatment within the target population are also prepared using the New Product assessment form but the SMC confidentially seek additional advice about the economic case for the companion diagnostic test from the Scottish Genomic Test Advisory Group (SG-TAG) or Scottish Pathology Network (SPaN), as appropriate [302].

The SMC does not routinely meet with the applicants/sponsors prior to submission. However, if unsure about whether the medicine is within the remit of SMC or the type of submission required, the applicant/sponsor can complete a company information request form and return to the secretariat [303]. Based on the information submitted, SMC will provide guidance on submission requirements. The SMC does offer early engagement meetings to support applicants when specific requirements are met, such as when aspects of the submission suggest there would be mutual benefit from a meeting to discuss concerns or issues relating to SMC process or policy, or when the medicine has Ultra Orphan designation or is included in the Early Access to Medicines Scheme (EAMS) or in the Innovative Licensing and Access Pathway (ILAP) [304-306]. Where a pharmaceutical company has a query on submission requirements that is not clearly addressed in the guidance documents on the website, they can contact the SMC Secretariat by email for advice [303].

Canada

CADTH undertakes reviews of medicines and issues reimbursement recommendation and/or review reports to all participating Canadian "drug programs" (federal, provincial, and territorial medicine programs (excluding Quebec) and cancer agencies that participate in CADTH's review processes and Canadian Blood Services) [49]. CADTH's recommendations are nonbinding. Reimbursement decisions are made by each medicine program based on CADTH's recommendation and including other factors such as the medicine plan's mandate, jurisdictional priorities, and financial resources. Medicines eligible for review by CADTH are new, have a new indication, new combinations of two or more medicines, new formulations of an existing medicine and subsequent-entry products for non-biological complex medicines. Generic medicines and biosimilars are not typically reviewed through CADTH's reimbursement review processes. The clinical utility of companion diagnostic tests are considered with the same standard/complex submission for assessment as the codependent medicine. Submissions may be sponsored by industry, oncology groups or medicine programs. Submissions can be lodged either prior to or after receiving market authorisation from Health Canada.

To increase efficiency, CADTH carries out the following reimbursement review types depending upon the intervention under assessment: standard reviews, tailored reviews, and complex reviews. The output of CADTH's review of a submission is a reimbursement recommendation document. In October 2022 CADTH changed it standard review method. Prior to October 2022, this process was carried out by CADTH, based on

information supplied by the sponsor. After October 2022, a standard review consists of CADTH preparing a clinical report based on the sponsor's completed summary of clinical evidence template, source documentation provided by the sponsor, and stakeholder input; and an economic report based on an appraisal of the sponsor-provided pharmacoeconomic evaluation. The PICO for guiding the systematic review for inclusion in the submission are defined by the sponsor and provided in Section 2 of the submission. The Reimbursement Reviews procedures guidance and clinical evidence template provide guidance on selection the appropriate PICO elements for the review protocol [49, 307].

In situations where a potentially eligible sponsor does not file an application (e.g., submission, resubmission, or reassessment) through CADTH's sponsored reimbursement review process, public drug programs may request a non-sponsored reimbursement review from CADTH's Formulary Management Expert Committee (FMEC) [181]. For a medicine to be considered for non-sponsored review:

- the medicine must be in the later stages of the technology lifecycle,
- there should be enough clinical evidence available to allow CADTH to evaluate the effectiveness of the medicine,
- generic or biosimilar drugs are available,
- the reference drug did not have a previous CADTH reimbursement review for the indication of interest and/or new evidence has emerged and the sponsor declines to file a resubmission or reassessment with CADTH, and
- it must have received a positive reimbursement recommendation internationally.

The review process comprises of specifying a protocol (i.e., PICO) and then conducting one or more independent systematic reviews according to the protocol and a cost comparison between the medicine and the appropriate comparator(s). In this case the evaluation is carried out by CADTH and CADTH develop the review protocol including the PICO [181].

For the province of Quebec, HTA is carried out by the Institut national d'excellence en santé et en services sociaux (INESSS) [308]. For a health product (medicine, medication administration device or blood product) to be eligible for registration on the List of Medications of the RGAM, on the List of Medications - Institutions or on the Liste des produits du système du sang du Québec (List of Québec blood products, in French only) or reimbursed by another public mechanism (e.g., dedicated program), a sponsor must submit a listing application. To ensure a more coordinated process regarding recommendations by INESSS and CADTH, requests for evaluation can be submitted to both organisations at the same time. This synchronized approach is critical to ensuring efficient evaluations as part a synchronised evaluation process by Health Canada, CADTH and INESSS.

In Canada, both CADTH and INESSS offer pre-submission meetings to facilitate the efficient preparation and filing of a medicine submission and have similar processes [49,

[308]. These meetings are at the request of the sponsor, and the topic is dictated by the sponsor. CADTH limits sponsors to one meeting per submission. Once a submission has been filed with CADTH, it is no longer eligible for a pre-submission meeting. Sponsors may request a pre-submission meeting with CADTH for a submission to be filed within 12 months of the meeting. To ensure maximum value from the discussion, sponsors are encouraged to schedule the pre-submission meeting at least 20 business days prior to the anticipated date the application will be filed. Sponsors must prepare a pre-submission briefing paper to provide CADTH with the information required to prepare for meeting. The briefing paper is intended to provide a concise summary of key issues and questions. Sponsors are limited to one meeting per submission and the meeting should be held less than 12 months prior to filing the submission. Guidance documents from INESSS suggest that significant issues must be identified by the applicant when putting together the evaluation request to justify a pre-submission appointment, e.g., clinical issues such as uncertainties on clinical data, the choice of comparator, the connection between primary objective and overall survival, quality of life, the medicine's position in the clinical pathway, and the requested reimbursement indication [308] For CADTH, sponsors must prepare a pre-submission briefing paper providing a concise summary of key issues and questions. INESSS have similar requirements regarding the provision of information in advance of the meeting [49, 308].

South Korea

The Health Insurance Review and Assessment Service (HIRA) is a public agency that is commissioned by the Ministry of Health and Welfare to review the comparative effectiveness and cost effectiveness of any new medicines submitted for listing and to determine the price for generic medicines. The submission to HIRA, including supporting evidence of comparative effectiveness and cost effectiveness of the medicine, is prepared by the sponsor. HIRA staff review and comment on the submitted evidence for subsequent deliberation by the Pharmaceutical Benefit Coverage Assessment Committee (PBCAC) [20, 309]. The PBCAC is an independent advisory committee whose role is to make recommendations on benefit coverage for HIRA.

There is no guidance available in English about how the scope of the assessment and development of PICO criteria are undertaken in South Korea. There was no information suggesting that a separate scoping process is undertaken for PICO development or about the availability of pre-submission meetings between a sponsor and HIRA. There was no evidence that a separate scoping process is undertaken for PICO development or about the availability of pre-submission meetings between a sponsor and HIRA.

Cell and gene therapies are evaluated in the same manner as medicines [310]. However, if a new medicine has no viable alternatives, it is considered an "essential drug", and may be exempt from requiring a pharmacoeconomic evaluation (instead, basing its list price on the lowest price used in one of seven reference countries) [310]. Where the long-term clinical outcomes are uncertain, a risk-share agreement may be developed. It is unclear

whether this pathway (where a pharmacoeconomic evaluation is exempt) has a different process for developing PICO criteria.

There is no dedicated process for evaluation of companion diagnostics. The medicine and companion diagnostic are considered in parallel by HIRA and the National Evidence-based healthcare Collaborating Agency (NECA). HIRA assesses the medicine and NECA evaluates the companion diagnostic test. There was no information available regarding determination of the PICO criteria for each codependent component [311].

Taiwan

The National Institute for Health Technology Assessment (NIHTA) was established by the Center for Drug Evaluation (CDE) to carry out HTA requested by the National Health Insurance Administration (NHIA). They consider comparative clinical efficacy, cost effectiveness and budget impact of the medicine in addition to evaluating applicability to Taiwan. The assessment report is completed within 42 days and submitted to the NIHA to support the decisions on National Health Insurance (NHI) reimbursement made by the NHI Joint Meeting for Pharmaceutical Benefits and Reimbursement Scheme.

No separate process for PICO development was reported. However, a systematic review of the evidence of relative clinical effectiveness and safety is included in the assessment report and research questions are developed to guide the assessment and the economic analysis.

There was no information presented about the provision of pre-submission advice that might impact on the PICO. The applicant provides the submission, but the assessment is carried out by the HTA team. Variations in PICO/research question development were not reported.

Variations based on technologies of interest

In many key jurisdictions, the sponsor initiates the process of having a medicine evaluated, meaning that the process for identifying which medicines to assess is reactive. However, there are exceptions to this. Austria, Belgium, Ireland, Luxembourg and the Netherlands have created the Beneluxa Initiative on Pharmaceutical Policy with the aim to give patients faster access to innovative medicines. The members of the initiative use Horizon Scanning of medicines upcoming for marketing authorisation and invite the companies to submit a joint submission to two or more member states. It is unclear whether there is a separate PICO development step in these assessments.

INVOLVEMENT OF STAKEHOLDERS IN THE DEVELOPMENT OF THE PICO

With respect to the involvement of stakeholders in the development of the PICO, the following question was used:

Is there any involvement of clinicians (HCPs (Health Care Professional)), sponsors/industry, public, patients, regulatory agencies or other advisory bodies in determining PICO?

The most common stakeholders involved in developing the PICO, are the sponsor of the medicine being assessed, with advice provided by jurisdictions' governments, regulatory or HTA agencies (Table 22). In addition to this, most jurisdictions have input from healthcare professionals. Those jurisdictions with a separate scoping phase are able to incorporate more stakeholder input than those without a scoping phase. Following their assessment of the level of comprehensiveness of HTA practices around the globe, Oortwijn et al [312] reported that scoping is often not part of the HTA process. They considered that scoping should be recommended as it plays an important role in obtaining evidence that is appropriate to stakeholders and is likely to increase the relevance and feasibility of HTA implementation for stakeholders.

Table 22 Stakeholder involvement in the development of the PICO

Country	Organisation	HCPs	Sponsors/ industry	Public	Patient groups	Regulatory agencies	Other advisory bodies
Australia	PBAC	●	●	●	●	●	●
Australia	MSAC	●	●	●	●	●	◑
England	NICE	●	●	●	●	●	●
Wales	AWMSG	○	●	○	○	○	○
Scotland	SMC	●	●	○	○	○	○
Europe	EUnetHTA	●	●	●	●	●	●
France	HAS	●	●	●	●	○	●
Germany	G-BA and IQWiG	●	●	●	●	◑	●
The Netherlands	ZIN	○	●	○	○	○	○
United States	ICER	●	●	●	●	○	●
Canada	CADTH	●	●	●	●	●	●
Canada (Quebec)	INESSS	○	○	○	○	○	○
South Korea	HIRA	○	●	●	●	○	●
Taiwan	NIHTA	○	●	●	●	○	●

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; MSAC = Medical Services Advisory Committee; NICE = National Institute

for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Australia

In Australia, the selection of the PICO components for therapeutic medicines is guided by advice in the *PBAC Guidelines*, the requested PBS listing and proposed listing restrictions, and the clinical claim [285]. Although sponsors may have consulted healthcare professionals during development of the clinical trial and/or dossier preparation, no formal process of consultation on the PICO criteria is mandated for the purposes of the submission to PBAC. This may occasionally result in instances where stakeholders other than sponsors, would prefer that a different/broader indication be assessed, but there is no ability for this to occur under the current pathway (i.e. the sponsors are required to make the submission, rather than there being a pathway where an HTA report on the medicine can be produced independent of the sponsor, like there is for technologies assessed by MSAC). The Therapeutic Goods Administration (TGA) is involved with defining the population (at is broadest) and the intervention (dosing regimen). The population in whom treatments are effective is frequently broader than the population in whom the treatment is cost-effective, at a price that is considered acceptable by the sponsor. This can result in narrower PBS restrictions than TGA registered indications, due to pricing constraints.

For technologies assessed by the MSAC, including blood products and screening programmes, the standard pathway is for there to be a separate scoping phase to develop the PICO criteria, which are considered PASC. PASC comprises of healthcare professionals and a member of the Consumer Health Forum [313]. During this process, the application form is made available for written stakeholder input. The exception to the PASC process, is if the Department of Health and Aged Care and the MSAC executive determines that the application can bypass PASC. This occurs when the PICO criteria included in the application form are very clear, or if a very similar topic has been recently assessed. Alternatively, if a post-market review is performed (such as occurred for Immunoglobulin), then a Review Reference Group may be established to provide input on the PICO criteria.

If a pharmaceutical requires a codependent test to select the relevant patients to receive a targeted therapy, then stakeholder input on the test component is received through consultation on the application form (which is made available to the public), and through discussion by PASC [289, 290, 314].

Highly specialised technologies may be evaluated by either the MSAC or the PBAC, depending on whether they are an inpatient treatment (assessed by MSAC) or an outpatient treatment (assessed by PBAC). Where medicines are initiated as an inpatient treatment, but then transition to chronic management as an outpatient and this accounts for the majority of the treatment provision, they are considered by the PBAC.

Stakeholder input on vaccines to go on the National Immunisation Program (NIP) is discussed in the Assessment of Vaccines section of this paper. Vaccines that go on the PBS (such as travel vaccinations) are assessed in the same manner as undertaken for medicines.

A summary of the committees and whether additional stakeholder input (through targeted or public consultation) is sought to develop the PICO criteria for different technologies in Australia, is shown in Table 23.

Table 23 Summary of committee and other stakeholder input into PICO criteria in HTA system in Australia

Technology	HTA Committee(s)	Committee input into PICO	Additional stakeholder input on PICO	Funding arrangement
Medicines	PBAC	Only as feedback during evaluation of submission	No	PBS or LSDP[1]
Outpatient highly specialised therapies for PBS	PBAC		No	PBS (Highly Specialised Drugs Program)
Vaccines for PBS	PBAC		No	PBS
Vaccines for NIP	ATAGI and PBAC	ATAGI	No	NIP
Test-medicine codependent technologies	MSAC and PBAC	PASC (for test component)	Yes	MBS and PBS
Technologies for MBS	MSAC	PASC	Yes	MBS
Inpatient highly specialised therapies for NHRA	MSAC	PASC	Yes	NHRA
Blood products	MSAC	PASC	Yes	National Products Price List

ATAGI = Australian Technical Advisory Group on Immunisation; CAR-T = chimeric antigen receptor – T cell therapy; LSDP = Life Saving Drugs Program; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NHRA = National Health Reforms Agreement; NIP = National Immunisation Program; PASC = PICO Advisory Sub Committee (of the MSAC); PBS = Pharmaceutical Benefits Scheme

[1] PBAC do not make recommendations regarding listing through the LSDP, but medicines are only assessed for the LSDP after being rejected for listing on the PBS.

Jurisdictions with a separate scoping stage for the PICO

England

Participation of stakeholders in the scoping process that defines NICE's assessment framework and issues for consideration (PICO criteria) is considered important by NICE to ensure that the scope has been informed by an appropriate level of expertise [27]. NICE

identifies stakeholders before they consult on the draft scope or hold a scoping workshop. A patient and carer organisation or professional organisation qualifies as a stakeholder if it works at a national level (covering the UK or England, or a UK branch of an international body) and represents patients, carers or healthcare professionals either broadly or directly related to the technology being considered. Other stakeholders include the technology sponsor, NHS commissioning groups and specialist centres that manage care in conditions with small patient populations. When there is no patient or carer organisation working at a national level for the technology being considered, as defined above, NICE may request and approve an international organisation becoming a stakeholder in the evaluation at its discretion. Stakeholders also include research organisations with an interest in the technology, developers or distributors of a relevant technology, providers of NHS services in England, organisations that cover the whole NHS such as the NHS Confederation, patient and professional organisations covering Northern Ireland or Scotland or Wales only, and relevant comparator and companion diagnostic test companies. Other organisations may be included as stakeholders when appropriate [27].

After drafting the scope, further consultation occurs with a Public Involvement Programme [315]. NICE sends the draft scope and stakeholder list to stakeholders for comment and asks them if there are other organisations that need to be included in the consultation [27]. As well as patient and carer organisations, they may also consult interest groups representing specific ethnic groups and disability advocacy groups. The draft scope and list of stakeholders is then published on the NICE website. The length of consultation depends upon the complexity and uncertainty about the draft. Stakeholders are invited to comment about whether the technology is suitable for a cost-comparison evaluation during the scope consultation [27].

If the topic covers a new disease area or care pathway that NICE has not evaluated before or recently, or there are uncertainties about the evaluation that a workshop could address, NICE may hold a scoping workshop . NICE invites stakeholders to send representatives to this workshop. The workshop includes discussions on whether the scope in appropriately defined, the appropriateness of completing an evaluation and the appropriate evaluation process and can discuss issues raised by stakeholders during consultation. The company can provide preliminary details of the evidence it will submit in the evaluation and discuss any evidence gaps that may cause uncertainty at the scoping workshop. NICE updates the scope, considering the comments received during consultation, and the discussions at any scoping workshop. If it is clear during scoping that a topic is not suitable for evaluation, NICE may decide not to proceed with the evaluation [27].

Europe (as a single jurisdiction)

At the time of this scoping review being performed, member European countries were participating in the framework set out by project EUnetHTA 21 (2021-2023), in which

Joint Clinical Assessments (JCAs) and scoping pilots were conducted[30] . For a JCA, the scoping process was started by the sponsor providing the claimed indication, dosage, and route of administration [316]. The aim of the scoping process was to identify the relevant PICO(s) for the assessment scope.

The EUnetHTA JCA Secretariat then created a PICO survey to distribute to member states to collect information about individual states needs in terms of the PICO parameters. Member states then incorporated input from patients and clinical experts into their responses to the survey, which were then consolidated to form one or more PICO sets. This was then reviewed by patients and clinical experts and validated at a JCA Committee for Scientific Consistency & Quality (CSCQ) meeting [316].

The preferred method for patient participation was to collect patient input for joint assessments in the scoping phase. The patient input could inform development of the PICO criteria and provide insights into patient experiences. Patient organisations were invited to submit their input through an open call on EUnetHTA's website or via direct contact from assessment teams to European or national umbrella patient organisations or specific European or national patient organisations. EUnetHTA provided a Patient Group Submission Template in different European languages for patient feedback. In the open call, EUnetHTA asked general questions about patient views on the disease, important outcomes to be considered in the assessment, and expectations about the medicine being assessed [297].

Other feedback may be gathered via individual or group discussions or an online scoping meeting.

EUnetHTA also sought healthcare practitioner (HCP) input during both the scoping and assessment phases. They considered that clinicians who have collaborated with the manufacturer or the other pharmaceutical companies as having conflicts of interest. The pool of clinical experts to consult with could, therefore, be small, particularly in rare disease fields [297]. Industry have expressed concern that this may be too restrictive and risk the most appropriate experts being unable to be involved [297]. Participation in (e-)meetings, reviewing of drafts, and direct contact (Q&A) during all phases of the assessment were recommended methods. For assessments with short timelines, the Q&A approach was the preferred method. HCP were able to provide feedback on the research questions and PICO shared with them during the e-meeting.

United States of America

In the USA, ICER initially have targeted stakeholder input, and then provide a draft scoping document for further input from stakeholders. In an effort to improve equity,

[30] The EUnetHTA 21 framework is subject to change as the official procedural guidelines for JCAs under the European HTA Regulation are currently being developed (2023-2024). The Regulation will be implemented from January 2025 *(personal correspondence from IQWiG received February 2024).*

they are also taking steps to expand their patient input to include a greater diversity of the community, such as including the Black Women's Health Imperative, the National Hispanic Health Alliance, and the National Coalition for LGBTQ Health [317].

Jurisdictions without a separate scoping process for the PICO.

Scotland

In Scotland the PICO criteria are not tabulated within the submission form but the elements that form the PICO criteria are outlined in the form, with guidance regarding selection of these criteria. There is no explicit public, patient, or HCP input into the development of the PICO criteria included in the submission. However, comments from stakeholders during the evaluation period may guide consideration of the PICO elements included in the sponsor's submission. Section 8 of the submission form completed by the sponsor includes contact details for relevant patient groups and information about the submission [302]. The Summary Information for Submitting Patient Groups Form is circulated to these patient groups so that they can prepare a Patient Group Submission for consideration in parallel with the sponsor's submission during the evaluation process [318, 319]. Ideally, the information is gathered from people in Scotland who may benefit from receiving the new medicine. Patient Groups are supported by the SMC Public Involvement Team through the submission process by email, phone or MS Teams [320]. They may read the draft submission and highlight any areas which could be strengthened. Patient groups have between 6 to 8 weeks - from when the assessment is announced - to complete and return their submission. The Patient Group submission is provided to committee members as part of the meeting papers and a summary is presented during the main SMC committee meeting by one of the Public Involvement Team. A summary of the patient group submission is included in the final Detailed Advice Document (DAD) [318].

Once a submission is entered into the workflow, an assessment team reviews the submission. This often includes an e-mail exchange of questions and answers with the submitting company which could include questions about the scope of the assessment, including the PICO criteria. Assessment teams complete both clinical and economic checklists, which, with the original submission and clinical expert comments, go to the New Drugs Committee (NDC), who reviews the evidence and makes a preliminary recommendation to the SMC committee.

European Union countries

In France, there is no explicit input into the development of the PICO criteria prior to assessment. If the evaluation justifies it, stakeholders may be contacted to provide advice to the Committee, before or during the meeting where the medicine is considered. This includes external experts, or other stakeholders or interested parties

to complement the scientific expertise [257]. The optional early scientific advice (during trial development) from HAS staff can involve additional experts and patients [101].

In Germany, sponsors, HTA and regulatory groups may interact "early" (during study development) and "late" (during compilation of the dossier). Since 2019, when the Act for More Safety in the Supply of Pharmaceuticals was introduced, there has been a requirement for indication-related data collection (through existing registries) and more engagement with medical societies [321]. Interested people or organisations are invited to provide comments on early benefit assessments, but it is unclear what stakeholder input is involved in the development of the PICO criteria.

In the Netherlands, advice is provided by CVZ, but it is unclear whether other stakeholders are involved in the development of the PICO criteria. If conditional approval is sought for a medicine addressing a disorder with an unmet clinical need, then medical professionals and patient associations must be involved in developing a study protocol [300].

The European Patients' Academy (EUPATI) provide guidance for how patients can be involved throughout the medicines research, regulation and HTA process [322]. They recommend that patients are involved in the scoping phase of HTAs through written submissions and involved in oral consultation meetings to discuss the HTA scope. To facilitate patient involvement, templates, guidance documents and telephone support should be provided, and consideration should be given to compensation for the time required.

Canada

Since October 2022, for sponsored reimbursement reviews the medicine submission is provided by the sponsor (without a separate review protocol stage) [49]. There is no opportunity for input into defining the PICO criteria prior to submission except for the attending clinician representative(s) during a pre-submission meeting if one is requested by the sponsor.

In situations where a potentially eligible sponsor does not file an application (e.g., submission, resubmission, or reassessment) through CADTH's sponsored reimbursement review process, public drug programs may request a non-sponsored reimbursement review from CADTH's Formulary Management Expert Committee (FMEC). Stakeholder engagement during the non-sponsored reimbursement review will occur in the same manner as sponsored reimbursement reviews, with some minor amendments. In addition to patient and clinician input, there is a call for industry and medicine program input into the non-sponsored review. Clinical expert(s) provide guidance on development of the review protocol (including the PICO) [181].

CADTH does offer a pre-submission meeting at the sponsor's request. Sponsors may bring consultants and/or clinical experts as representatives. CADTH recommends that a relevant Canadian health care professional participate in the pre-submission meeting.

For example, a clinical specialist who has expertise on the disease and the available treatments in Canada, particularly in the case of an unmet medical need. These meetings are not open to patient group representatives.

A call for patient and clinician group input is posted 29 days prior to the expected date of a submission, and is open for 35 business days [323]. Patients' perspectives, experiences and values are integrated formally in the CADTH processes through the patient group input procedure. Patient input is submitted to CADTH by patient groups [324]. Individual patients or caregivers are encouraged to work with a patient group that represents their condition. All patient group input received for the medicine under review is collated by CADTH. The complete patient group input is incorporated into the CADTH report(s). The patient group input submissions in their entirety are included in the committee brief and a summary of the patient input discussion at the committee meeting is included in the recommendation documents. Clinicians providing input on behalf of a group or association use the clinician input template [325]. This template has questions and prompts to help guide respondents to provide the information that will be most helpful to the review team and the expert committees in their work. The clinician group submissions are posted on the website and are consolidated in the CADTH report.

Responses are summarised by CADTH and provided back to the person/group who submitted input to check the summary is accurate. This information is no longer used to influence the development of the PICO criteria (as these are developed by the sponsor in their submission) but can be used during the appraisal and interpretation of the evidence [49].

INESSS also invites citizens, patients, caregivers and health professionals, as well as their associations and groups, to participate in the consultation on medicines that will be subject to scientific evaluation [326]. Experiential data, reported mainly by health professionals, patients and caregivers, contribute to the process of determining therapeutic value and enable INESSS to document the actual clinical experience of the medical condition and the treatments. The consultation period begins four weeks before the date targeted by the sponsor for submitting its request for evaluation, for an overall total of seven weeks. While it is unlikely that the stakeholder feedback would guide the evaluation framework and PICO presented in the submission, it may influence the evaluation of the evidence provided. Information is gathered in many ways, such as working groups and within the context of the consultation process for medicines to be evaluated by INESSS. It can also be obtained by means of a scientific literature review or another recognised consultation method, such as a survey using standardised questionnaires, focus groups or semi-directed interviews. This input by stakeholders is made public as part of the evaluation process and may be included in the recommendation made to the Minister of Health and Social Services by INESSS [326].

South Korea

There is no evidence that stakeholders outside of the sponsor or their representative have input into the assessment scope. The development of a PICO and stakeholder involvement is not discussed in the available documents on HIRA's website. Patient input seems to be restricted to consideration of the submission evaluation by the PBCAC. The PBCAC is composed of experts in medical subspecialties, pharmaceutical science, statistics, and health economics. Consumer advocacy groups, patient groups, and government officials are also included [309]. Even though representatives from citizens/consumer groups participate in the committee, it is difficult for them to represent public views at meetings because of their relatively low numbers. A patient group had the right to nominate one member to the PBCAC. However, because patient groups are perceived as having COIs – as many are supported by pharmaceutical companies - and so there has been some debate about patient groups being represented on the committee [309].

Taiwan

The opportunity for stakeholders to have input into defining the research question and PICO development prior to the assessment is discussed on the CDE website. Stakeholder feedback seems to occur during the assessment phase and while under committee review.

Clinical experts are consulted during the assessment about the current clinical landscape (clinical practice, usage, and possible comparators).

In Taiwan, patients participating in HTA and the reimbursement decision-making process are fully supported by the NHIA. There are guidelines developed by the CDE/HTA group to support the provision of patient opinions during HTA [132]. Patient involvement is encouraged via a patient online platform, group conversations, and other methods. The CDE/HTA team retrieves and summarises opinions received via the online platform and incorporates them into the HTA report. The report is published before the PBRS Joint Committee meeting, allowing stakeholders to learn about patients' experiences. Two patient representatives are members of the committee. However, it is difficult for the two representatives to adequately represent patients' opinions on all products included in an agenda because of the short time frame from posting the committee meeting agenda. However, the CDE/HTA has invested resources in improving patient organisation involvement in HTA [132].

There is no information about the involvement of other groups (e.g., consumers).

CONSIDERATIONS FOR DETERMINING POPULATION(S)

With respect to the population selected for inclusion in the PICO, the following were considered:

- Is any advice/guidance provided?
- Does the population have to match the pivotal trial?
- Is the (proposed) registered indication considered?
- Can the reimbursed indication be different to the (proposed) registered indication?
- Does guidance around PICO explicitly require consideration of population subgroups?
- Is there guidance around subgroups determined by test results (biomarkers, imaging etc)?
- Are equity considerations regarding Population mentioned?

Table 24 Guidance, policies and conventions for determining the target population for medicines

Country	Organisation	Guidance	Pivotal trial	Registered indication	Reimbursed indication	Guidance around subgroups	Equity
Australia	PBAC	●	◑	●	●	●	●
Australia	MSAC	●	◑	●	●	●	●
England	NICE	●	●	●	●	●	●
Wales	AWMSG	◑	○	●	○	○	○
Scotland	SMC	●	◑	●	◑	●	●
Europe	EUnetHTA	●	●	●	●	●	●
France	HAS	◑	●	●	●	●	●
Germany	IQWiG	●	●	●	●	●	●
The Netherlands	ZIN	●	●	●	◑	●	●
United States	ICER	●	○	●	○	●	●
Canada	CADTH	●	○	●	●	●	○
Canada (Quebec)	INESSS	●	○	●	●	●	○
South Korea	HIRA	●	○	○	○	●	○
Taiwan	CDE	●	○	●	○	●	○

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Only subtle differences were identified in the guidance on the population provided by each jurisdiction, which were unrelated to the process of developing the PICO criteria (with a separate scoping phase or without). The guidance provided by different jurisdictions has therefore been grouped below by geographical area, rather than by process.

Australia

In Australia, the submission developed by the sponsor includes the PICO criteria. The *PBAC Guidelines* provide advice that the target population should be relevant to the clinical claim and Australian clinical setting [285]. TGA registration is required before being marketed. However, consideration for registration may occur in parallel with the evaluation of a PBAC submission (parallel process). If the approved TGA indication is different from initially requested, the evaluation of the PBAC submission will check whether the population requested in the submission is fully within the final TGA registration. This can be inefficient due to discrepancies, and a resubmission may be required if the population issue cannot be resolved during the evaluation. It is possible for the target population to be narrower than the registered indication, such as when the cost-effectiveness of the intervention differs between subgroups.

The population should at least overlap with the participants characteristics in the key trial(s). A subgroup of a trial population can be selected but must be justified (e.g. presence of a biomarker that is an effect modifier, or if a subgroup has more severe disease, with a higher clinical need). If a trial population is broader than the requested reimbursed population, *PBAC Guidelines* request that results for the whole trial population be provided, as well as the relevant subgroup, and the complement [285].

Population subgroups may be identified by an existing investigative test already available on the MBS or may require a codependent submission to obtain MSAC approval for MBS listing of the test. Equity of patient access is considered by both PBAC and MSAC when considering reimbursement (e.g., lack of access to the investigative test could impact on equity of access to the codependent medicine). If a codependent test is being evaluated, the testing population must be specified (as it will differ from the treatment population) and be ratified in the PICO confirmation by PASC [290].

For applications being made to the LSDP, the population must be considered ultra-rare (≤1 for 50,000 people). Submissions to the LSDP must therefore provide Australian prevalence data from a reputable source as evidence of meeting this criterion, as well as evidence that the condition is associated with a significant reduction in age-specific life expectancy [292]. The LSDP Expert Panel determines the eligibility for the medicine, which may result in a different population than requested by the sponsor.

England

In England, NICE defines the population during the scoping process [27]. The scope may identify subgroups where the effectiveness or cost-effectiveness may differ from the overall population, or subgroups who require special consideration. The indications approved or expected to be approved for marketing authorisation will be influential in defining the population but could be broader than the population assessed for reimbursement. However, populations outside of the market authorised indications are excluded from assessment. NICE acknowledge that there may be populations who could benefit from the proposed technology who are not included in the assessments but, as resources are limited, so the patient populations need to be defined carefully to make best use of the evaluation.

Something being explored by NICE is whether a distributional cost-effectiveness framework may be used to consider inequality [327, 328]. This requires examination of background levels of inequality across different groups (such as quintiles of socio-economic status, or by race), and consideration of how the intervention will benefit/harm each of these subgroups. Different subgroups are therefore considered, based on equity-related measures. It is unclear whether these subgroups would be outlined during the scoping phase.

A guidance document on a value framework being trialled by NICE for antimicrobials acknowledges the difficulty in defining the relevant population(s) and subgroups for new products, as the marketing authorisation may be focused on pathogens rather than indications for use [329]. For antimicrobials, there is unlikely to be a single indication, rather, they are likely to be used against a wide variety of pathogens. Consideration should be given to the setting of antimicrobial use (community, hospital or restricted to intensive care use), as the rate of infections and transmission dynamics will differ based on the setting. The benefits of antimicrobials extend beyond the patients treated, to the wider population, so the perspective of the evaluation needs to be explicit [329]. This means considering the benefit to those who do not become infected (due to the antimicrobial stopping transmission), the benefit to those treated with antimicrobials who are able to have other treatments and procedures (e.g. chemotherapy, organ transplants, and surgical procedures), and those who have resistance and may not have existing treatment options in the absence of the new antimicrobial. In this manner, rather than the cost per patient treated, the assessment should capture the value for the population overall.

Wales

In Wales, the All Wales Medicines Strategy Group (AWMSG) only evaluate medicines with UK marketing authorisation, excluding any “off-label” uses of licensed medicines. The applicant may highlight a subpopulation within the submission for which the medicine may be more effective but must ensure that evidence is provided to support use in this subpopulation. The guidance for submissions requests a definition of the

population and the number of patients eligible for treatment in Wales, including the data source [330].

Scotland

In Scotland, the population (or any subgroup of the population) should be within the market authorisation for the medicine. If a subgroup of the marketing authorisation population is used, this should be justified (e.g., presence of a biomarker). A submission based on a subgroup of the market authorisation population would be considered a selective submission and the assessment decision would only cover the subgroup (selective population). Under these conditions, the reimbursed population would be different (a subgroup) of the market authorisation population [331]. Sponsors are requested to identify any equity issues in their submissions.

Europe (as a single jurisdiction)

In Europe, for JCAs under the EUnetHTA 21 framwork, the sponsor provided the claimed indication (based on the population applied for in the submission to the EMA), and the member states defined the relevant populations and subpopulations to be included in the dossier [316]. They could also request exploration of potential modifiers within the population (e.g. age, sex, dose, background treatments etc). The JCA Committee for Scientific Consistency & Quality (CSCQ) considered the specific requests made by the member states. However, given the scoping process occurs before the Conformité Europenne (CE) marketing indications are finalised, there is the possibility that the population may change if the Committee for Medicinal Products for Human Use (CHMP) of the EMA recommended a different indication / intended use from the one initially applied for. The PICO were then required to be updated [316].

European countries

In France, there is little guidance by HAS about defining the patient population. The trial population should be consistent with the population proposed for reimbursement [332]. Any subgroups presented should be pre-planned in the study protocol. A comparison of HTA strategies across jurisdictions reported that although a large proportion of submissions to HAS are reimbursed as per the regulatory label, the reimbursed population can also be narrower than the regulatory label [37].

In Germany, reimbursement of medicines occurs after marketing authorisation, for the identical population [332]. At the point of early benefit assessment, subgroups may be defined, if comparators differ for different subgroups.

In the Netherlands, the population can deviate from the registered indication, if it is more narrow. Subgroups may be identified. However, even if the claimed therapeutic value/cost-effectiveness is only for a single sub-population, sponsors should provide data for the entire indicated (registered) population. The dosing and method of

administration must be as per the summary of product characteristics. Equity is not explicitly mentioned as a consideration for outpatient medicines. If applications are made for conditional approval for orphan medicines, conditional and exceptional[31], the population eligible would be the same as the registered indication from marketing authorisation.

USA

ICER suggest that the population may be defined to align with current or anticipated FDA indications[333]. ICER have recently published a White Paper on advancing HTA methods to increase equity [317]. They consider that equity can be improved by a range of measures, from:

- choice of topic - considering whether the technologies involve underserved communities with the potential to reduce health disparities;
- subgroups chosen to include in the Population, such as race/ethnicity and socioeconomic status/location, by considering the likelihood of subgroup effects; and
- who is involved in the scoping process - including diverse patient groups and facilitating input so that location is not a barrier, trying to learn about the experiences of diverse groups of patients and understand their views of the potential impact of the intervention under review on health equity.

Canada

CADTH suggest that the population is defined as the full population approved or proposed by the regulatory agency, Health Canada, unless otherwise decided, in consultation with CADTH [49, 307]. If the requested population is for a subgroup of the Health Canada indication, the systematic review should still be for the full Health Canada indication. For the cost-utility analysis, the base case analysis reflects the Health Canada–approved indication. For a specific subgroup of the indicated population or if there are any relevant subgroups, these must be provided as scenario analyses. For reassessments, the base-case analysis must reflect the scope of the reassessment. Subpopulations identified in the sponsor's reimbursement request should be pre-specified in the protocol as a subgroup(s) of interest and results reported where available. Other relevant subgroups that are likely to be of interest to clinicians, medicine plans, patients, and those included in the sponsor's pharmacoeconomic submission should also be included in the protocol. These should be based on clinically important prognostic factors, confounders, or modifiers of treatment effects. For a reassessment, the systematic literature review should focus on the population that is

[31] See definitions in Glossary

relevant to the sponsor's request for revised reimbursement criteria for the medicine under review [49, 307].

For INESSS, the population should reflect the approved or proposed indication approved by Health Canada. If a more restricted population is proposed for reimbursement (subgroup) justification for selection of the subgroup is required and supporting clinical evidence [308].

South Korea

No guidance on defining the relevant population was identified from the South Korean HTA agency.

Taiwan

In Taiwan, the target population should be that of the approved indication/recommended health insurance coverage. Off label use is excluded. Defined subgroups can be considered in addition to the target population. No discussion was reported in the available information about subgroups defined by biomarkers or treatment equity considerations [334].

CONSIDERATIONS FOR DETERMINING COMPARATOR(S)

With respect to selection of comparator(s), the following were considered:

- Is there explicit advice (guidance) on comparator selection? E.g., should it be the most cost-effective? Most used?
- Is the comparator defined?
- Is the choice of comparator based on clinical practice?
- Is the choice of comparator based on cost?
- Is the choice of comparator based on prior reimbursement decisions?
- Are multiple comparators used?
- Is the clinical comparator used as a reference for pricing purposes?

HTA is inherently comparative in nature, analysing how clinically effective and cost effective the proposed technology is against at least one alternative. Deciding what comparator to use can have a large influence on the results of the clinical evaluation, economic analysis, and conclusions of a report.

In jurisdictions where there is no separate scoping process, national guidelines rarely specify whether the comparator is defined before or during the assessment of a new pharmaceutical.

Most countries require that the proposed pharmaceutical is compared against the current standard of care. In Australia, UK, Canada, France, Germany and the Netherlands, the comparator must be an accepted therapy for the condition of interest.

PICO criteria are normally used to define the scope of the clinical evaluation, and to determine the comparator against which the cost-effectiveness is determined. However, the comparator used for the clinical and cost-effectiveness analyses may not always align with the reference treatment used for pricing decisions, which can either include alternative treatments for the same indication available in the same jurisdiction, or it can be the proposed new medicine pricing used in different jurisdictions.

Table 25 Guidance, policies and conventions for determining the comparator for medicines

Country	Organisation	Guidance	Defined	Clinical practice	Based on Cost	Prior reimbursement decisions	Multiple comparators	Pricing reference
Australia	PBAC	●	●	●	◑	●	●	◑
Australia	MSAC	●	●	●	●	●	●	◑
England	NICE	●	●	●	◑	●	●	●
Wales	AWMSG	●	●	●	○	○	○	○
Scotland	SMC	●	●	●	◑	●	●	○
Europe	EUnetHTA and EMA	●	●	●	●	◑	●	○
France	HAS	●	●	●	●	●	●	◑
Germany	IQWiG	●	●	●	◑	●	◑	◑
The Netherlands	ZIN	●	●	●	●	●	●	●
United States	ICER	●	●	●	●	○	○	○
Canada	CADTH	●	●	●	○	●	●	◑
Canada (Quebec)	INESSS	●	●	●	●	●	●	◑
South Korea	HIRA	●	●	●	●	●	●	◑
Taiwan	CDE	●	●	●	○	○	●	◑

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Australia

For submissions to the PBAC, a main comparator needs to be nominated, with the option of also including secondary comparators [285]. The main comparator should be the therapy most likely to be replaced by the proposed medicine in clinical practice. In most cases, this will be a current PBS-listed medicine prescribed to treat the same target population. If the proposed medicine is for a population without a currently listed PBS medicine, or the proposed medicine will be used in addition to – rather than replace – a medicine, the comparator would usually be standard medical management, which could include a non-listed medicine, a surgical procedure, best supportive care, or conservative management. Multiple comparators may be required if there are subgroups for whom the main comparator is not an appropriate treatment. The PBAC specifies that the comparator is what is likely to be replaced, rather than what should be replaced (meaning that if current practice differs from best practice, preference is given to current practice being the comparator). The *PBAC Guidelines* also request that any near market comparators be considered (i.e. medicines likely to enter the Australian market for the same population at the same or an adjacent PBAC meeting).

When a cost-minimisation claim is being made and there is more than one alternative therapy, the PBAC may request, consistent with the *National Health Act 1953*, to have the lowest cost product in the 'basket of products' considered for pricing decisions, regardless of the frequency of use. If the new medicine is significantly more expensive than the lowest cost product, the PBAC can only make a positive recommendation if, for some patients, the new medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy [285].

If the comparator has a risk share arrangement in place, the sponsor of the new medicine would usually share the same conditions as the comparator.

The MSAC guidelines state that the comparator should ideally have had its cost-effectiveness established [290]. If the comparator is funded through the MBS then it may be reasonable to assume the cost-effectiveness of the comparator. If not, then MSAC may require that the cost-effectiveness of the comparator is established before the cost-effectiveness of the intervention can be considered. The requirement to establish cost-effectiveness can be discussed with PASC during the PICO Confirmation process. Advice may also be provided on a case-by-case basis by the MSAC Executive.

England

When selecting the most appropriate comparator(s), NICE recommend the following items are considered:

- established National Health Service (NHS) practice in England
- the natural history of the condition without suitable treatment
- existing NICE guidance

• cost effectiveness of the comparator

• the licensing or regulatory status of the comparator.

Comparator technologies may include branded and non-proprietary (generic) medicines and biosimilars. They may also include technologies that do not have regulatory approval for the population defined in the scope if they are established in clinical practice for the population in the NHS. When considering an 'off-label', 'unlicensed' or 'unregulated' comparators, the amount and quality of evidence, particularly for safety and efficacy, for the unregulated use will be considered for decision-making. Technologies that NICE has recommended for managed access programs are *not* considered established practice in the NHS and are not considered suitable comparators. Sometimes both the technology and comparator or standard care are part of a sequence in the care pathway. In these cases, the evaluation may compare alternative sequences [27].

A framework for evaluating antimicrobials suggests that new antimicrobials would normally be used in addition to standard practice (so the comparator would be standard practice alone) but that standard practice is likely to vary widely across jurisdictions depending on local resistance levels, the cost of antimicrobials, clinician behaviour and other factors [329]. Where an organism has antimicrobial resistance to multiple antimicrobial medicines, there may be no 'active' comparator available.

As antimicrobials may be used for a wide range of different indications, there can be a variety of comparators based on the infection site, pathogen, and mechanism of resistance, and whether the treatment is used in the microbiology-directed or empiric setting (i.e. after testing the susceptibility of the pathogen, or on the basis of clinical suspicion of the pathogen and its mechanism of resistance) [335]. For example, two antimicrobials assessed by NICE using a new value framework and a subscription-style funding model (discussed further in Paper 4), had 6 to 9 different comparator treatment combinations (although evidence was not available for all of these).

Scotland

Similar comparator criteria are used by SMC as by NICE [331].

Europe

In Europe, the EMA have specified the importance of an active comparator in marketing authorisation applications. Their definition of an adequate active comparator has been defined as "the gold-standard, EU-licensed product for the appropriate indication and line". Some countries in Europe have national legislation which has formal requirements on the choice of comparator. This includes Austria, Croatia, Czech Republic, France, Germany, Latvia, the Netherlands, Norway and Poland [336].

In EUnetHTA JCAs, member states were expected to nominate comparators that suit their clinical needs and legislation. Comparators could be either registered treatments

or off-label, with the option of multiple comparators [337]. Pricing is not determined at the EU level.

In France, HAS state that the comparator must be clinically relevant and publicly funded at the time of assessment. Multiple comparators are allowed. For pricing purposes, the improvement in actual benefit (versus the comparator) is used for price negotiations, as is the price of alternatives medicines with the same clinical purpose, and prices observed in Germany, the UK, Italy and Spain [338]. If there is no improvement (or worsening) in benefit versus the comparator, then a biosimilar may be given the same price as the comparator without requirement for economic evaluation.

In Germany, initial funding of medicines occurs after approval of medicines by either the EMA (for Europe-wide approval) or the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (for German approval). Market access approval is based on the risk/benefit profile of the technology and that does not require use of an active comparator. However, to be eligible for continued funding, an early benefit assessment is performed against the standard of care for the condition, based on a dossier provided by the time of first marketing. The appropriate comparator therapy can either be one specific treatment, or multiple treatment options. The G-BA prefers comparators that have already been established as having patient-relevant benefit. When the medicine of interest is an orphan medicine (not exceeding an annual revenue of EUR30 million), then the comparator may be the comparator from the pivotal study [332]. Companies may request advice on the appropriate comparator from G-BA. The status of the comparator (whether a generic or under patent-protection) impacts on price negotiations [339]. A retrospective analysis by Boucard-Maitre et al (2021) reported that although Germany and France's policies regarding comparators are similar and the appropriate comparator chosen may be the same for particular interventions, IQWiG would consider only those studies where the intervention was directly compared with the prespecified comparators, whereas HAS in France was more flexible in regards to the type of evidence they accepted [340].

In general, economic analyses are not required for new medicines in Germany, but can be requested by G-BA if the price negotiation between SHI bodies and sponsors fail [341]. The framework for the health economic evaluation is specified in §35b SBG[32] V and §139a SGB V. The appropriate comparator for the reference case is the therapy used in the benefit assessment procedure for the demonstration of added benefit. If there are equally appropriate comparators, then separate analyses are conducted to take into account the different costs of the comparators (in particular the cheapest and most expensive treatments). The appropriate comparator should be established in practice and not excluded by the efficiency principle. Other comparators may also be considered,

[32] SBV V = Sozialgesetzbuch – Fünftes Buch – Gesetzliche Krankenversicherung (Social Code Book – Book V – Statutory Health Insurance)

and a new benefit assessment including these comparators may be required. When health economic evaluations are performed outside the framework defined by §35b SBG V, a cost-effectiveness ratio can be plotted as one or more efficiency frontiers, comparing the benefits of multiple treatments for a therapeutic area graphically against their benefits.

In the Netherlands (for reimbursement of out-patient medicines), the comparator needs to be the treatment regarded as the first choice in daily practice, where its efficacy has been proven. If a medicine is used in practice for an indication for which it does not have market authorisation, it may still be used as a comparator [342]. Since 2021, the Netherlands have used an International Reference Pricing rule using Belgium, France, Norway and the UK as a reference basket of countries to determine the maximum pricing [343] (therefore the clinical comparator does not directly influence the price of the new medicine).

United States of America

In the USA, ICER select relevant comparators through a survey of clinical guidelines, consultation with clinical experts, and reviews of clinical trials. Active comparators (rather than placebo) are prioritised where feasible [333].

For Medicare in the United States, most medicines are reimbursed without considering evidence against an active comparator (i.e., clinical data used for registration with the Food and Drug Administration is normally compared against placebo) [344].

Canada

In Canada, CADTH state that relevant comparators may include: treatments currently reimbursed by at least one participating medicine plan for the indication under review; reimbursed treatments that are currently off-label in Canadian practice; or treatments that have previously received a recommendation by CADTH in favour of reimbursement. All relevant comparators need to be included in the submission unless CADTH have agreed that one or more relevant comparators may be excluded. Comparators may also include non-medicine comparators (e.g. transfusion plasmapheresis) [49].

INESSS provide guidance that the preferred comparators are those that will be replaced or shifted by the new medicine. If the comparator is another medicine, it must be listed in the regular section of the List of Medications, in the List of Medications – Indications, or in the list of exceptional medications with a recognised indication relevant to the new medicine. If there is no available treatment then a placebo may be used as comparator. If the primary comparator (or the comparator in the pivotal study) is not marketed in Canada, not included on the lists, and has not been reviewed or evaluated by INESSS, then the sponsor must submit a review of the scientific literature in order for the safety and effectiveness of the proposed comparator to also be reviewed [308].

In Canada, therapeutically novel medicines can be priced no higher than the median of the reference basket of international countries which include Australia, Belgium, France, Germany, Italy, Japan, the Netherlands, Norway, Spain, Sweden and the United Kingdom [345]. It is only in situations where no reference prices are available, that the maximum price is based on domestic prices of therapeutically similar medicines [346]

The comparator chosen for the clinical assessment therefore does not directly influence the price negotiations for the new medicine, even in the case of non-inferiority.

South Korea

In South Korea, guidelines state that the comparator should be the recommended standard treatment in medical practice (the treatment with the largest market share). If two or more treatments have similar market share, multiple comparators may be used. For pricing purposes, if the new medicine is non-inferior to the comparator, and there are multiple alternatives available for the same indication, the price of the new medicine will be set at the weighted average of the alternatives (weighted based on the market share) [147]. Where there is no alternative treatment available, pricing will be based on an adjusted average price of the new medicine in the USA, UK, Germany, Japan, Switzerland and France. If a pharmacoeconomic exemption is given due to limited clinical evidence, the lowest adjusted price of the reference countries is used [147].

Taiwan

In Taiwan, the comparator(s) selected should be a reimbursed medicine which is the existing medical technology likely to be replaced by the intervention and is most used based on China's clinical practice (rather than Taiwan's). The current standard treatment (such as surgery, supportive therapy, etc.) is selected for the comparison. Multiple comparators may be used. When there are multiple comparative products, the following selection conditions are considered: medicines with the same pharmacological effect or the same therapeutic category; medicines with a head-to head comparison study; medicines that have been used by the most patients or used the most in recent years; or the first choice recommended by current clinical treatment guidelines [334].

Pricing negotiations are conducted as a separate step from the HTA, by the Pharmaceutical Benefit and Reimbursement Scheme Joint Committee. Most new medicines are priced with reference to the comparator (with or without a markup depending on whether there is an added benefit or not). Where there is direct evidence comparing the new medicine against the best available medicines in the market and there is a modest improvement in clinical efficacy, the reference medicine may be a similar medicine for the same therapeutic class listed within the past 5 years (to avoid benchmarking against an older product with a much lower price) [31]. New medicines with a modest improvement in clinical efficacy or similar efficacy to existing medicines, are

capped at the median prices of the reference countries (USA, UK, Canada, France, Belgium, Germany, Japan, Sweden, Australia and Switzerland [31].

Other jurisdictions

Most jurisdictions require the comparator to be the standard of care according to clinical practice or national or international guidelines, and thus the therapy most likely to be replaced. This includes Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, Iceland, Ireland, Israel, Italy; Mexico, New Zealand, Norway, Poland, Portugal, Scotland, Slovak Republic, Slovenia, Sweden, Switzerland and Turkey [344] [332]. Some of these jurisdictions are also explicit that the comparator should be a treatment which is already reimbursed (Australia, Czech Republic and Poland). One exception to this is AEMPS (The Spanish Agency of Medicines and Medical Devices), which state that the comparator in the RCT described in the dossier should represent standard of care, and if it does not, then the comparator is based on cost-effectiveness/efficiency criteria [332]. This is similar to Greece which requires the comparator used in the key trial. Hungary requires the most frequently used and cheapest to be the comparator [344].

Discussion on comparators

A review of 29 pharmacoeconomic guidelines reported that 86% recommended the comparator be "the standard of care for local practices" [347]. Sacristán et al. (2020) made some interesting observations around the history and consequences of using "standard of care" as the basis for a comparator. They noted that the starting point for standard practice is often a historical inheritance of a set of interventions without a strong evidence base, many of which were selected for reasons other than evidence of the impact on population health (such as the severity and rarity of the condition) [348]. If the standard of care has not had its efficiency assessed or has only been assessed versus non-efficient alternatives, the results of subsequent cost-effectiveness analyses could be biased in favour of the new intervention [348].

This can be illustrated by comparing two different disease areas. In the area of oncology, many interventions are only marginally better than the (on-patent) most recent treatment used, and much more expensive, but the incremental cost effectiveness may be easy to demonstrate. In other disease areas, there may only be off-patent low-cost treatments available, against which it may be hard to demonstrate cost-effectiveness due to the large differential price between an off-patent treatment and a new on-patent medicine [348]. This can create perverse incentives such that there is further development of medicines in areas where recent progress has been made, rather than in areas where no new developments have occurred in recent years.

One possible alternative to the problem of different starting points, is creating an independent reference of "doing nothing". This approach has been proposed by the World Health Organization (WHO), as a means of comparing the costs and benefits of mutually exclusive interventions (such as comparing screening versus vaccination) [348].

However, the generation of evidence on the natural history of conditions, when there are effective treatments are available, would be unethical, so the data are often difficult to obtain, except perhaps through registry data. Sacristán et al. (2020) did not suggest replacing the use of active comparators with comparators of doing nothing but considered it a useful additional approach to help avoid starting-point biases and problems with "historical inheritance". Natural history registry data have their own limitations in terms of ensuring comparability with the population receiving the new treatment. However, recent methodological developments in creating synthetic cohorts may be able to address some of these once methods become more reliable and may have utility for estimating comparative effectiveness for rare diseases against 'natural history' or for medicines compared to off-patent treatments that are in wide use in the community [349].

CONSIDERATIONS FOR DETERMINING OUTCOMES

When determining outcomes of interest, is there guidance on:

- appropriate outcomes?
- use of Patient Reported Outcome Measures (PROMs)?
- surrogate outcomes (without translation)?
- outcomes beyond the treated individual?
- non-health outcomes?
- other outcomes?
- minimal clinically important differences (MCIDs)?

The topic of what outcome measures different jurisdictions preferred and accepted was discussed in more journal articles than other aspects of the PICO criteria. This therefore meant that the summary of how jurisdictions approached outcome measures was more suited to a grouping by topic than by jurisdiction.

Nevertheless, Table 26 summarises what was found on outcome measurement in the guidance documents from HTA agencies in different jurisdictions.

Table 26 Guidance, policies and conventions for determining the outcomes for medicines

Country	Organisation	Appropriate outcomes	PROMs	Surrogate outcomes	Beyond the treated individual	Non-health outcomes	Other outcomes	MCIDs
Australia	PBAC	●	●	●	●	●	●	●
Australia	MSAC	●	●	●	●	●	●	●
England	NICE	●	●	●	●	●	●	●
Wales	AWMSG	○	○	○	○	○	○	○
Scotland	SMC	●	●	●	●	○	○	○
Europe	EUnetHTA / HTACG	●	●	●	● in JCAs	● in JCAs	● in JCAs	●
France	HAS	●	●	●	●	●	◑	●
Germany	G-BA and IQWiG	●	●	●	●	●	●	●
The Nether-lands	ZIN	●	●	●	●	◑	●	●
United States	ICER	●	●	●	●	●	●	●
Canada	CADTH	●	○	○	○	○	○	○
Canada (Quebec)	INESSS	●	●	●	●	●	●	●
South Korea	HIRA	○	○	○	○	○	○	○
Taiwan	CDE	●	○	●	○	○	○	○

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; JCAs = Joint Clinical Assessments; MCID = minimum clinically important difference; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; PROMs = Patient reported outcome measures; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Appropriate outcomes

Common to all HTA groups is the consideration that the assessment of health benefits should include patient-relevant outcomes, such as mortality, morbidity and quality of life.

In Europe, for JCAs, part of the scoping process was for Member States (MS) to request what health outcomes they would like to include in the JCA. In the JCAs, the outcomes

should not be ranked, as the clinical relevance or interpretation of importance may differ between member states. Guidance from EUnetHTA made the distinction between patient-level outcomes (including the specific outcome measurement instrument), population-level summary measures (or summary statistics), and effect measures (the statistics used to express the effectiveness between treatments/groups). During the scoping process, defining the outcome as a concept (without further specifications on the method of measurement) increased the likelihood that the sponsor could provide at least one result relevant to that outcome. They recommended that if a Core Outcome Set (COS) was available for the population of interest, that these outcomes be considered. Other health outcomes, considered relevant by patients, health practitioners or HTA groups could complement the use of a COS.

CADTH state that the outcome measures used should reflect those used in the clinical trials [49]. ICER give only broad guidance, that health outcomes (i.e. changes in symptoms or conditions that people feel and affect quantity or quality of life) are prioritised, but that relevant intermediate outcomes and non-clinical outcomes may also be reviewed (other measures of societal benefit)[333].

Composite response endpoints

Bespoke composite response endpoints are becoming more common to measure treatment response for multisystem diseases in trials and observational studies [350]. CADTH considers that composite outcomes are generally not satisfactory to inform treatment effect estimates and that pharmacoeconomic evaluation should be based on relevant individual outcomes [49]. In Australia, PBAC requires that the components of a composite outcome are justified and that the true estimates of the disaggregated components are provided so that the driver (if any) of the outcome can be determined [285].

Patient Reported Outcome Measures (PROMs)

Patient reported outcomes are those related to the status of a patient's health condition or treatment that come directly from the patient. They can include health-related quality of life (HR-QoL), functioning, symptoms (both disease and treatment-related), patient satisfaction, and adherence to treatment [351].

Chassany et al. (2022) compared guidance documents from Germany, France and the UK, and considered that the impact of patient reported outcomes (PROs) in HTA decision-making is clearest in Germany, where assessments by IQWiQ and G-BA can include PRO data to demonstrate added benefit. [351]. Bartol et al. considered that patient-reported symptoms were not given the same prominence as mortality but also indicated that these were a growing consideration in benefit assessments [321]. Minor improvements in fatigue, nausea and vomiting scales and social functioning on the European Organisation for Research and Treatment of Cancer (EORTC) QLC-C30 have been found to contribute to added benefit ratings [351]. IQWiG have been sceptical of

carer-reported outcomes on behalf of patients, as it has been argued that these reflect the needs of the carer rather than the needs of the patient [352].

In France, HAS states that evidence demonstrating HR-QoL contributes to a higher clinical added value rating [351]. However, HAS has been cautious about the use of PROs where the studies are open label, where there are significant missing data, or where the HR-QoL data are considered exploratory [351]. HAS requires HR-QoL benefit to be demonstrated using validated instruments and have stated a preference for the EuroQol – 5 Dimension (EQ-5D) or Health Utility Index [351].

NICE considers that PROMs can capture important aspects of conditions and interventions (such as health related quality of life, performance status, symptom and symptom burden and outcomes such as anxiety and depression). In NICE evaluations, the preference for cost-effectiveness analyses is to use the EQ-5D to determine utilities. The impact on PROs other than the EQ-5D has been limited in NICE assessments [351].

In Scotland, the SMC recommend that for assessment of ultra-orphan medicines (for conditions affecting fewer than 1 in 50,000 people), the sponsor should collect PROMs, and any other data on the impact of the medicine, beyond the direct health benefits.

The *PBAC Guidelines* suggest that if multi-attribute utility instruments (MAUI) or other patient-reported outcome measures (PROMs) are used, details need to be provided. Sponsors are requested to consider whether all important disease- or condition-specific factors that might be relevant are captured in the outcome measure [285].

Although ICER in the USA did not have any explicit guidance around the use of PROMs, this could be because extensive guidance is not required when the assessment is performed in-house, rather than by sponsors. The lack of guidance does not mean that PROMs are not used.

Surrogate outcomes

A study by Smith et al (2022) aimed to understand the impact of different efficacy endpoints on reimbursement decisions for oncology products made by health technology assessment (HTA) bodies [353]. Recent analyses suggest that manufacturers' traditional focus on overall survival (OS) may be in decline due to the growing acceptance of surrogate outcomes as a basis for EMA regulatory approval [354, 355]. EMA oncology product marketing authorisations were screened to identify products that completed review by three HTA bodies during 2016–2019: United Kingdom's NICE, Germany's Federal Joint Committee (G-BA), and France's HAS. Each decision's endpoint information, including OS and progression-free survival (PFS), was extracted. Results showed that for added benefit ratings, the mature OS remains the most important endpoint to HTA agencies, although the presence of PFS data and its maturity or statistical significance were also positively associated with a full reimbursement. These findings are consistent with prior analyses demonstrating that OS was the gold standard for achieving a positive HTA decision in Germany, France, and the United Kingdom [356].

In principle, the acceptability of surrogate endpoints to G-BA, HAS, and NICE is heavily dependent on demonstrable correlation (or strong association) between the surrogate and with a hard clinical endpoint such as that demonstrated between PFS and OS for some cancers. In practice, this correlation has been achieved in only a handful of solid tumour types [357-359]. Smith et al (2022) reported a trend toward fewer oncology products presenting mature OS data over time suggesting that sponsors may be increasingly confident in achieving reimbursement with surrogate endpoint data, although mature OS data provided the strongest correlation to positive reimbursement decisions [353]. This trend highlights the dichotomy in how regulatory bodies such as EMA and FDA are incentivising innovation through rapid market authorisation for new products based on limited data, while HTA bodies place a lower value on these limited data (e.g. immature OS) for reimbursement decisions [354, 355]. This partly because regulators need to make a simple qualitative decision as to whether the clinical benefits outweigh the risks of the medicine or technology. This contrasts with the HTA agency or payer perspective which is about making a quantitative decision on the *magnitude* of clinical benefit and, thus, whether there is sufficient value demonstrated by the outcomes reported to spend taxpayer funds on the medicine or technology in question, as opposed to spending it on other areas of the health system (the opportunity cost).

An international review of the methodological guidelines of 73 HTA agencies found that 40% made specific reference to consideration of surrogate outcomes [360]. PBAC and MSAC (Australia), EUnetHTA, NICE (England), IQWiG (Germany), CADTH, INESSS and NACI (Canada), AOTMiT (Poland), the Portugese National Authority of Medicines and Health Products (INFARMED) all have detailed prescriptive criteria for the accepted use of surrogate endpoints (requiring validation of the surrogate by trials linking the surrogate endpoint with the final endpoint).

PBAC Guidelines in Australia specify that surrogate outcomes should be presented only when it is critical to the therapeutic conclusion or economic evaluation. The surrogate outcome should be transformed to a patient-relevant outcome unless the PBAC has previously accepted the surrogate outcome as being valid (with some additional restrictions around the size of effect, the surrogate having been transformed in the same population, and the proposed medicine is in the same class as the medicine for which the surrogate outcome was previously validated). When treatments for rare diseases are being assessed, it is acknowledged that data might not be available to link a surrogate outcome to clinically relevant outcomes. Guidelines for submissions for the Life Saving Drugs Program state that at a minimum, the biological plausibility of an appropriate surrogate to survival should be provided [292].

For codependent tests assessed by MSAC, surrogate outcomes are acceptable if they have been validated as being able to predict patient-relevant outcomes. If adequate direct evidence is available, surrogate outcomes are not required[290].

NICE considers that for a surrogate endpoint to be validated, there needs to be good evidence that the relative effect of a technology on the surrogate end point is predictive

of its relative effect on the final outcome. This evidence preferably comes from a meta-analysis of level 1 evidence (i.e., RCTs) that reported both the surrogate and the final outcomes, using the recommended meta-analytic methods (bivariate meta-analytic methods). However, any types of comparative evidence may be used to validate a surrogate outcome. A review of NICE assessments did not find any association between the use of a surrogate outcome and funding decision [361].

In Scotland, SMC prefers the comparative effectiveness of a medicine to be established using patient-relevant outcomes, however, they do allow the use of surrogates, and allow them to be primary outcomes.

In Taiwan, sponsors can apply for priority review and an accelerated approval pathway for new orphan medicines. These applications can be based on surrogate endpoints [51].

EUnetHTA provide guidance that surrogate outcomes can either be a biomarker (an objective measure of a biological, pathogenic or pharmacological process/response) or an intermediate outcome (a measure of a function or symptom that is not the final outcome of the disease). Surrogate outcomes should only be requested when their validity has been demonstrated. The EUnetHTA guidance discusses different "levels of evidence" regarding the certainty of the link between the surrogate and final outcome.

In a narrative review on surrogate outcomes, Dawoud et al. (2021) argued for more selective use of surrogate outcomes. When new medicines are given regulatory approval on the basis of surrogate endpoints, assessing the impact that the medicine has on patient relevant clinical outcomes become highly uncertain. It can also complicate treatment decisions as both clinicians and patients may misinterpret medicine effects on surrogate endpoints as being clinically meaningful. However, the strength of evidence available on the validity of the surrogate outcome needs to be balanced with the potential benefits and harms of a new medicine, particularly in areas of unmet clinical need [362].

The Australian Department of Health and Aged Care is collaborating with NICE (England), SMC (Scotland), CADTH (Canada), the Health Technology Assessment international (HTAi) Global Policy Forum, ZIN (the Netherlands) and the Colombian Institute for Technology Assessment in Health to develop more guidance on the use of surrogate outcomes when analysing cost-effectiveness, to assist sponsors understand how surrogate outcomes should be used [363].

Outcomes beyond the health of the individual

Health interventions for patients can impact on their families/carers as well. The PBAC and MSAC currently specify that the base case should only include treated individuals, but that health outcomes for others such as the family or carers may be included in sensitivity analyses. In France, one aspect of 'public health impact' is how the treatment/organisation of care affects a patient's family. Similarly, NICE state that economic evaluations should include direct health effects for patients and carers,

where relevant. This requires an assessment of carer health-related QoL [364]. However, even when carers' quality of life is considered a primary outcome or end point (such as a NICE evaluation of medicines for Alzheimers' disease), the economic models have not always included carers' outcomes, to the criticism of stakeholders [352]. ICER in the USA have a value framework that incorporates outcomes to caregivers, other patients, and the public. When ICER assesses interventions for ultra-rare conditions (fewer than 10,000 people in the USA), they give greater weight to the intervention's impact on patient and carer productivity, education, disability and other societal considerations[333]. ICER and the US Second Panel on Cost-effectiveness in Health and Medicine recommend conducting a parallel "societal" perspective for the cost-effectiveness analyses, so that all parties affected by the intervention can be considered [365].

Not every jurisdiction mentioned the inclusion of others. CADTH does not mention carers in their guidelines [364]. There was also very little indication available in English regarding whether carers/family member outcomes would be included in assessments in South Korea or Taiwan. In Germany, carers' outcomes are not considered the responsibility of the healthcare system and is given lower priority than outcomes for the patients being treated [352].

For transmissible diseases, modelling which focuses on an individual patient do not capture broader benefits of interventions. HTA agencies have historically had scarce guidance on evaluating antibiotic agents, antimicrobial agents, communicable diseases, and infectious diseases [366].

An article by Colson et al. (2021) argues that the way that HTA agencies determine the value of technologies is influential in giving signals to investors and manufacturers on what will provide a return on investment [366]. They therefore argue that HTA has a role in the international policy agenda of antimicrobial resistance. Most therapeutic technologies only benefit the individuals treated, whereas antimicrobial agents indirectly benefit the broader society [366]. Treating infected patients appropriately can reduce the demand for treatment for other patients, which should therefore be accounted for in financial and economic evaluations [366]. The proposal is that HTA agencies should develop explicit recommendations in their guidance documents on the importance of capturing community externalities associated with antimicrobial agents and other infectious diseases [366]. This includes accounting for reduced transmission rates, costs of treating resistant cases, quality adjusted life-years gained from avoiding infection, and performing sensitivity analyses on different levels of resistance (which are hard to predict) [367]. The *PBAC Guidelines* do include a section on the prudent-use principles for antimicrobial agents, including that data on the development of resistance should be provided in the relevant submissions [285].

In England, a framework for the value assessment of new antimicrobials has been developed and trialled for antimicrobials evaluated by NICE. In addition to outcomes relevant to standard medicines (effectiveness of treating the infection in the individual

and tolerance), they also outline elements relevant to antibiotics which are not included in traditional HTA including:

- transmission value (reducing overall incidence of an infection by reducing spread),
- insurance value (having treatments available in case of sudden, or major increase in incidence of infections),
- diversity value (reduced antimicrobial resistance due to 'rest period'),
- novel action value (new mechanism of action),
- enablement value (enabling treatment, e.g., prophylactic use in surgery or chemotherapy), and
- spectrum value (benefit of replacing broad spectrum with narrow spectrum antimicrobials that target specific pathogens) [329].

Data for these outcomes are expected to be derived from epidemiological studies or modelling studies, rather than trials.

Trials on antimicrobials have not historically collected much data on health-related quality of life, particularly at the population level [335]. Given that the population of individuals likely to receive the antimicrobials is heterogeneous, the benefits are also likely to vary to a large degree between individuals [335]. An article discussing learnings from the new assessment model used by NICE queried whether future HTAs on antimicrobials should consider a wide range of different scenarios rather than attempting to estimate the benefit for the average treatment-eligible population, and whether a simpler and more pragmatic approach may be sufficient [335].

Non-health outcomes

Outcomes other than the clinical benefit (safety, effectiveness), and cost-effectiveness may be considered in HTAs. The EUnetHTA core model includes the assessment of ethical, sociocultural elements, and legal elements, which are then referred to in national guidance, such as produced by HAS in France. ICER in the USA also include contextual considerations include ethical, legal or other issues, such as societal priorities.

Guidelines from the Netherlands have a section on forensic interventions, with interventions to target not only the mental health of the 'patient', but also to modify the environment, to alter their behaviour. Outcomes such as reoffending reduction, school performance or family functioning, and contact with the criminal justice system are provided as examples. Instead of quality adjusted life years, suggested outcome measures could be "criminal activity free years" or "drug abuse free years".

INESSS in Canada state that the repercussions of using the proposed medicine on the system's organisation is factored into the evaluation, such as the way care is delivered, and changes to whether the patient is treated as an in-patient or out-patient patient, and the accessibility of the medicine. If the proposed medicine has an impact on the

social system (impacting health professionals, the need to acquire any different resources, or use companion tests) this should be captured.

ICER in the USA have a value framework that incorporates not only comparative clinical effectiveness and incremental cost-effectiveness, but also potential other benefits/ disadvantages and contextual considerations. The other benefits/disadvantages include the impact of non-health outcomes for the individual, as well as outcomes related to the organisation. Although the base case economic evaluation is a health system perspective, for ultra-rare diseases, ICER have a modified framework, which includes also providing a model inclusive of societal costs, such as impact on patient and caregiver productivity, education, disability and nursing home costs [368].

In Australia, the *PBAC Guidelines* suggest that the submission may provide relevant information which could influence PBAC decision making (such as patient equity or access) and that there may some medicines and/or indications where nonhealth-related outcomes may be relevant to include, if supported by good quality evidence and sound reasoning [285]. More extensive guidance is provided for assessments for MSAC, with examples of the types of considerations which may have value to include, such as ethical analysis, organisational aspects, patient and social considerations, legal aspects, and environmental aspects [290].

It is unknown to what extent and how consistently these broader types of outcomes are incorporated into the clinical and economic assessments. Their incorporation can take a different skillset to the assessment of clinical outcomes and does take additional time.

Minimally clinically important difference (MCID)

An MCID is defined as the smallest change in score perceived as being an improvement or deterioration by a patient. The *PBAC Guidelines* suggest sources to search for an MCID, and state that MCIDs should be specified for the primary outcome (and if this is not the primary outcome), the main patient-relevant outcome. The MCID may be used to inform the noninferiority margin [369]. The MCID has traditionally been used for responder analyses, however, the Cochrane guidelines suggest that it can be used to help facilitate the interpretation of the results such as the difference between means [370].

EUnetHTA provide guidance on the interpretability of the outcomes, including concepts such as responder definition, and the minimal important difference (also called minimally clinically important difference). EUnetHTA consider that the most appropriate methods for estimating MCIDs are anchor-based based methods (linking changes in score to a patient global rating of change, or patient global impression of change). However, EUnetHTA also discuss other methods of estimating MCIDs, such as distribution-based methods, that consider responder definitions based on effect sizes, such as using Cohen's *d* and the rule of thumb where effect sizes of 0.2, 0.5 and 0.8 are considered small, moderate or large. An alternative is 1 standard error of measurement as a plausible MCID.

IQWiQ have explicit guidance that outcomes are considered clinically meaningful if the responder definition is ≥15% of the scale range (e.g. 15 points on a 0 to 100 visual analogue score) [351]. When response criteria are less than <15% of the scale range or no respond criteria are prespecified, then standard mean differences are used. An irrelevance threshold of 0.2 is used for results to be considered clinically meaningful [351].

Specific guidance on MCIDs was not identified from other key jurisdictions.

SPECIAL CONSIDERATIONS FOR THE DETERMINATION OF THE PICO

Are there special considerations/approaches for determination of the PICO for:

- populations or technologies of interest?
- technologies for rare diseases / for small patient populations where levels of evidence may be lower?
- populations for which there is a high unmet clinical need?
- vulnerable and/or disadvantaged patient populations?
- codependent technologies?
- emerging technologies with limited knowledge of long-term outcomes?

The topics of rare diseases and high unmet clinical need often overlap, as rare diseases are likely to have unmet need, due to a lack of effective treatments available. Many jurisdictions have variations in how they assess treatments for severe disease, where there is an unmet clinical need. Table 27 provides a summary of how HTA jurisdictional guidance has addressed special populations or technologies, including rare diseases.

Table 27 Variations in the guidance, policies and conventions for determining the PICO for special populations or technologies

Country	Organisation	Variation	Rare diseases	High unmet clinical need	Vulnerable populations	Co-deps	Emerging technologies
Australia	PBAC/LSDP	●	●	●	○	●	○
Australia	MSAC	●	●	●	●	●	○
England	NICE	●	●	●	○	●	●
Wales	AWMSG	●	○	○	○	○	○
Scotland	SMC	○	●	○	○	○	○
Europe	EUnetHTA/ HTACG	●	●	●	●	●	●
France	HAS	●	○	○	●	●	●
Germany	G-BA/	●	○	●	●	●	●

	IQWiG						
The Netherlands	ZIN	●	○	○	○	○	●
United States	ICER	○	●	○	●	○	○
Canada	CADTH	●	●	○	○	●	●
Canada (Quebec)	INESSS	●	●	○	○	●	○
South Korea	NECA	○	○	○	○	●	○
South Korea	HIRA	○	●	●	○	○	○
Taiwan	CDE	●	●	●	○	○	●

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; codeps = codependent technologies (test and medicine) = EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; LSDP = Life Saving Drugs Programme; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Rare diseases

Most jurisdictions have not implemented separate frameworks or processes for developing PICO criteria for medicines for rare diseases (DRD), instead adopting a flexible, pragmatic approach within their current HTA processes. These include CADTH, INESSS, NICE, HAS and ICER [89]. In Australia, the Life Saving Drugs Program (LSDP) provides access to treatments for ultra-rare[33] and life-threatening diseases with very expensive treatments [292]. All medicines on the LSDP must have first been considered by the PBAC. The process of developing the PICO criteria for the submission to PBAC is the same as a standard submission. A medicine must have been accepted as clinically effective by PBAC, but rejected for PBS listing because it does not meet the required cost effectiveness criteria before the applicant/sponsor can apply for the medicine to be funded through the LSDP. Relevant materials from the PBAC consideration (including ratified minutes/advice from the PBAC and its sub-committees, Pre-Sub-Committee and pre-PBAC responses from sponsors, and consumer comments received by the PBAC) are taken into consideration by the LSDP Expert Panel when the LSDP application is considered.

NICE assesses ultra-rare diseases (fewer than 1 in 50,000 or 1,100 people) via their Highly Specialised Technologies programme. This programme utilises the same methods

[33] Defined as fewer than 1 per 50,000 in Australian population

for scoping as NICE's standard technology appraisals and therefore the process for PICO development is the same [27]. The increased uncertainty around the evidence for rare diseases is accommodated by a departure from the standard appraisal process in that these technologies have a higher incremental cost-effectiveness ratio threshold[274].

The SMC assessment process for orphan medicine submissions is the same as for other medicine submissions [302]. Additionally, the Scottish Medicines Consortium (SMC) offers the submitting company the opportunity to request a Patient and Clinician Engagement (PACE) meeting if the decision is "not recommended" after the NDC meeting which gives patient groups and clinicians a stronger voice in SMC decision making for medicines used to treat end of life and/or rare conditions [371]. SMC also accept a greater level of uncertainty in the economic case recognising the limited evidence of efficacy. SMC have a separate process for ultra-orphan medicines (defined as fewer than 1 in 50,000 of the Scottish population) [372]. To be available through the ultra-orphan pathway the medicine must be validated as ultra-orphan by the SMC, meets SMC requirements for assessment under the ultra-orphan process, offers a Patient Access Scheme (PAS), and support the data collection arrangements for evidence generation. After the evidence generation period (up to three years), the company/sponsor provides an updated submission for reassessment by SMC regarding continuing use of the medicine in NHS Scotland.

CADTH allow a modified approach for medicines for rare diseases (defined as affecting fewer than 1 in 2,000 people) including greater use of non-randomised studies and greater engagement with the clinical community. However, the process of developing the PICO criteria remains the same as other medicines [49, 373].

In the USA, ICER have a modified framework for evaluating ultra-rare conditions (affecting <10,000 people in the USA), but the process for developing the PICO criteria is unaffected. Greater emphasis is placed on the societal impact of ultra-rare diseases (such as the productivity impact to the patient and caregivers, impact on education, disability and nursing homes) [368], so these should be incorporated into the outcomes listed in the PICO.

In Europe, Joint Scientific Consultations (JSC) are available for products which address unmet clinical needs (where there is no treatment or only unsatisfactory treatment available). This is frequently associated with rare, life-threatening or chronically debilitating diseases. Although these consultations provide non-binding advice prior to trials being performed, the topics discussed (such as appropriate comparators and outcomes) would influence the PICO used in the later submission. In the EU, orphan drug designation is available for treatments where the disease concerned is life-threatening or severe and rare, defined as no more than 5 per 10,000 people, where there is unmet need [374].

In Germany, orphan medicines undergo early assessment of benefit [163, 373]. For orphan medicines with revenues ≤EUR30 million per year, the sponsor is required to submit an abbreviated dossier to the G-BA (that does not require evidence of benefit over an "appropriate comparator therapy"). Although the additional benefit is automatically

assumed after market authorisation, the G-BA can still define the likelihood and extent of additional benefit ("minor", "consider", "major" or "not quantifiable", although they are not able to classify the medicine as "additional benefit not proven") [375]. For orphan medicines with revenues ≥EUR30 million in the previous 12 months, the applicant/sponsor must provide a standard submission for evaluation of benefit by IQWiG.

In France, HAS provides early access authorisation for severe, rare or incapacitating disease, where there is no appropriate treatment, and initiation of treatment cannot be deferred, efficacy and safety are strongly presumed based on results of clinical trials, and medicinal product is presumed innovative (compared against clinically relevant comparator). Early access status is granted for a fixed one-year period, with the opportunity for annual renewal. It is unclear what evidence is required to be collected during this period, or what requirements are for renewed funding. It is also unclear at what stage the PICO criteria for assessment are developed under this model, i.e., at the point of funding, to assist collection of appropriate data, or at the point of dossier submission.

In the Netherlands, orphan medicines approved by the EMA for severe conditions with an unmet clinical need, can apply for conditional inclusion in the basic health care package. This allows faster access for patients to potentially effective treatments, while data are being collected to demonstrate the clinical benefit (a condition of the conditional inclusion is that the sponsor must fund further research to be published within 7 years) [300]. However, if the cost is very high, the Minister of Health, Welfare and Sport can first place the product in a 'lock', which restricts reimbursement of the medicine until price negotiations can be carried out. It is unclear whether PICO criteria are developed to help specify what data should be collected during the period of coverage with evidence development.

In South Korea, a new medicine cannot be listed if price negotiations between the company and the NHIS fail, except for "medically necessary drugs". This category was created for medicines which are considered essential in treating patients where it meets all the following: 1) there are no alternative treatments; 2) the medicine is for a severe life-threatening disease; 3) the medicine is for a very rare disease; and 4) the health benefits of the medicine are supported by the evidence [376]. In these cases, another independent committee, the Benefit Coordination Committee, become involved in the pricing of the medicine [376] (similar to how a medicine may be considered for the LSDP after failing to be found cost-effective by the PBAC). However, the process for developing the PICO criteria and submitting evidence for therapies addressing an unmet need is the same as for other medicines.

Vulnerable and/or disadvantaged patient populations

There was very little guidance on special considerations for vulnerable and/or disadvantaged patient populations (with the exception of health inequity, in regard to

severe conditions with an unmet clinical need). As outlined in earlier in this section, some jurisdictions consider/prompt sponsors to consider the impact of new technologies on equity. At the time of developing the PICO criteria, consideration could be given to whether there are vulnerable and/or disadvantaged patient populations, who should be considered separately. England is considering introducing distributional cost-effectiveness analyses.

Benkhalti et al. (2021) have developed an equity checklist in HTA (ECHTA), which suggests that during the scoping phase, the problem should be defined (including questions such as "equity of what?", defining goals of i) equal access, ii) equal utilisation, or iii) reduced inequality in health), defining population subgroups through either a logic model and/or theoretical basis, and examining how the scope of the HTA could lead to potential biases for or against specific population groups [377]. They also suggest examining the opportunity cost of conducting an HTA on one topic versus another, and whether there is historical disadvantage (e.g., Indigenous populations), which might impact the choice of variables to assess. The checklist also provides questions on the stakeholders involved in the scoping process, whether the processes used may impede certain populations being adequately represented, and how to consider the diversity of patients [377].

Codependent technologies (companion diagnostics)

In Australia, most codependent technologies assessed have been medicine/test combinations where a related diagnostic test is required for patient selection and eligibility for a new medicine. The new medicine is submitted for listing on the PBS and the companion diagnostic is simultaneously submitted for listing on the MBS. Submissions can either be considered in parallel (separate submissions to each committee) or jointly (integrated submission considered by both committees) by MSAC and the PBAC [290]. Codependent technologies have a different process for determining the PICO criteria in Australia, compared to medicines without an associated test, as the testing component is evaluated by the MSAC, and goes through its subcommittee, PASC, to consider the scope [290]. Although the PICO criteria for both the test and medicine are outlined in a PICO confirmation document, PASC's remit is limited to providing advice on the PICO for the test and any codependency issues. PASC does not assess the PICO criteria for the medicine. The PBAC and MSAC provide guidance on how to evaluate the clinical utility of the companion diagnostic test, including whether the evidence suggests that the test findings are predictive of a treatment response rather than providing only prognostic or diagnostic information [285, 289, 290].

If a test being considered by MSAC is codependent, it is important to distinguish between the population eligible for testing and the population eligible for the treatment with the medicine or other therapeutic technology. If a codependent test–medicine combination is being assessed, then the 'intervention' describes what treatment the biomarker-positive patients *and* biomarker-negative patients would

receive. Comparators are required for both the medicine and the test. Outcomes are specified that are relevant for assessing each technology in the codependent pairing. Relevant outcomes for the companion diagnostic will include test accuracy and performance compared with the clinical utility standard, and relevant outcomes for the medicine component will be patient health outcomes. Health outcomes are defined for both test positive and test negative populations [290].

Of the key jurisdictions, South Korea, England, France, and Germany have guidance on codependent technologies, with additional outcome measures required to evaluate the testing component. However, the processes used for determining the PICO criteria are the same as for medicines without companion diagnostic tests.

NICE guidance for a new medicine/test combination is provided within the standard technology appraisal guidance [27]. Intermediate outcomes of the test are included in the assessment (diagnostic accuracy for biomarker and costs) and therefore these outcomes may be included in the PICO. Where the proposed test is not routinely available in the NHS, the associated costs of the diagnostic are included in the assessments of clinical and cost effectiveness as a sensitivity analysis [27]. Evaluations of multiple companion diagnostic test options is usually done in the NICE diagnostics assessment program [27].

In Scotland, if the medicine under review requires a diagnostic test (e.g. somatic, germline or biomarker test) in order to identify patients eligible for treatment within the marketing authorisation/target population and this represents a change in clinical practice, the submitting company provides additional information based on the data used in the economic and budget impact models [331]. The Molecular Pathology Implementation Steering Group has introduced a framework for decision making for tests in the Scottish Molecular Pathology Service [378]. The framework involves evaluation by the Molecular Pathology Evaluation Panel and final decision by the Molecular Pathology Consortium (MPC). MPC decision-making for new companion diagnostics is closely linked to SMC assessment [378]. Development of the PICO is not discussed in the guidance.

CADTH assesses evidence for the companion test supplied by the applicant/sponsor in the medicine submission and the price of the diagnostic test. The PICO is developed by the applicant/sponsor to guide searches for supporting evidence. The assessment of the clinical utility of the companion diagnostics under review is based on evidence supplied by the applicant/sponsor and reviewers may conduct additional literature searches. Assessment results are summarised in an appendix of the clinical review report. CADTH also consults patients and clinicians about the companion test. They may also consult experts in pathology and/or laboratory testing who are able to comment on front-line clinical aspects of companion diagnostics (e.g., the timing of biomarker testing in the clinical care pathway, the consistency of the testing protocol with current practice, and the availability of the testing) [49]. For INESSS, an evaluation of a companion diagnostic test must be submitted to the sector of Biologie médicale et génomique of INESSS. The

budget impact analysis of the medicine involved should include the size of the companion test population and an estimate of the cost of the test [308].

South Korea uses a similar approach to NICE and CADTH.

In Germany, IQWiG has guidance on the evaluation of tests for biomarkers used within the framework of personalised or better stratified medicine [379]. This applies both to biomarkers determined before the decision on the start of a treatment (or of a treatment alternative) and to those determined during treatment to decide on the continuation, discontinuation, switching, or adaptation of treatment. Internal assessment is carried out by the methods assessment subcommittee of the G-BA. The appraisal is carried out by the plenary session of the G-BA [173]. The initial biomarker tests for *EGFR* inhibitors were partially funded by pharmaceutical companies, which meant that a code was not provided in the pre-AMNOG reimbursement system. However, in 2017, a process was set up so that submission of a dossier for an oncology treatment involving a biomarker for treatment selection, triggers an adjustment to the outpatient statutory health insurance Uniform Assessment Standard Tariff at the same time as the benefit assessment decision is performed, so that the companion biomarker test can be reimbursed [321]. There is still no formalised reimbursement scheme for biomarker tests in the inpatient sector [321].

In France, some codependent technologies are included in the "coverage with evidence" development program [173]. EUnetHTA have a discussion paper on appropriate study designs for examining personalised treatments (i.e., looking at both the biomarker and medicine). This provides additional guidance for codependent submissions.

Emerging technologies with limited knowledge of long-term outcomes

Emerging technologies such as cell and gene therapies are often approved based on accelerated approval pathways, which allow for surrogate outcomes to be used rather than final endpoints [380]. As discussed in the earlier section on determining outcomes, the use of surrogates normally requires validation, such as demonstration of the link between surrogate and final outcomes in meta-analyses of randomised trials in the population of interest. However, cell and gene therapies are often used in rare diseases, where validation is unlikely to have occurred. This makes assessing the value of these technologies very difficult. All the jurisdictions which have special processes for emerging technologies require data collection on patient outcomes to continue after conditional reimbursement. However, this approach only collects data on patients treated with the new medicine, not on those receiving "standard of care" (the comparator). Naïve indirect comparisons may be required to estimate the comparative safety and effectiveness, using historical or synthetic cohorts. Any regulatory conditions associated with a new medicine (such as requirements for safety/efficacy data capture), will have an impact on how the PICO criteria are defined. For emerging novel therapies, this may be a process of continuous development.

In the USA, ICER has provided guidance on the importance of patient-centric outcomes such as daily functioning, chronic pain, physical activities and goal attainment. The evidence generated for cell and gene therapies is predominantly single arm, due to small patient populations, or practical or ethical concerns due to the hope of a cure from the new treatment [380].

Recent changes to pre-assessment processes in Australia and internationally

Reforms to HTA processes in recent years are associated with the following:

- Collaboration (between jurisdictions, with the aim of reducing duplication of work by sponsors)
- Faster access (in general, or specifically for innovative treatments which address an unmet clinical need)
- Greater emphasis of real-world evidence collection after reimbursement

These reforms have implications for the determination of the PICO criteria to varying degrees (Table 28).

Table 28 Recent changes in the guidance, policies and conventions for determining the PICO for medicines

Country	Organisation	Recent changes	Due to emerging technologies	For faster access
Australia	PBAC	●	●	●
Australia	MSAC	●	●	●
England	NICE	●	●	●
Wales	AWMSG	●	○	○
Scotland	SMC	●	●	●
Europe	EUnetHTA / HTACG	●	●	●
France	HAS	●	●	●
Germany	G-BA/ IQWiG	●	●	●
The Netherlands	ZIN	●	●	●
United States	ICER	●	NA	NA
Canada	CADTH	●	○	○
South Korea	NECA	●	NA	NA
South Korea	HIRA	●	NA	NA

Taiwan	CDE	●	NA	NA

AWMSG = All Wales Medicines Strategy Group; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation; EMA = European Medicines Agency; HAS = Haute Autorité de santé; HIRA = Health Insurance Review and Assessment Service; HTACG = HTA Coordination Group of the Regulation on health technology assessment; ICER = Institute for clinical and economic review; INESSS = Institut national d'excellence en sante et an services sociaux; IQWiG = Institute for Quality and Efficiency in Health Care; MSAC = Medical Services Advisory Committee; NA = not applicable; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; ZIN = Zorginstituut Nederland (National Health Care Institute)

● Yes ◑ Partial ● No ○ Not reported/No information found

Changes to pre-assessment process in Australia

In 2022, the Australian Department of Health put out a consultation paper with a proposal for a cost recovered pathway for MSAC applications. As part of this proposal, sponsors may choose whether to bypass PASC (thus shortening the time to submission by approximately 4 months). Sponsors may benefit if this leads to earlier reimbursement, but there is a risk that a submission which includes incorrect PICO may be rejected for public funding, or deferred until further information is provided [288].

Collaboration

In 2022 (with updates in July 2023), it was announced that that the Australian Government Department of Health and Aged Care (PBAC and MSAC) would partner with the UK (NICE, Scottish Health Technologies Group; Health Technology Wales and All Wales Therapeutic and Toxicology Centre), Canada (CADTH and INESSS) and New Zealand (Pharmac) to explore implementing joint clinical assessments [381, 382]. NICE and MSAC currently have a scoping phase to determine the PICO and seek stakeholder feedback, whereas the other organisations rely on the sponsor to develop the PICO as part of their submission. In collaborating, it is unknown if whether a scoping phase will be used or not, similar to the process of JCAs performed by EUnetHTA, to ensure that the comparators used are relevant to each member agency.

From 2006, EUnetHTA have developed and piloted methods and processes for cross-border collaboration on HTA in Europe, including >20 joint clinical assessments (JCA) for medicines [383]. The goal of the EU HTA regulation is to improve access to life-saving innovative technologies [384]. Since 2016, the EUnetHTA JCAs and assessment by EMA have been aligned [385]. From January 2025, the implementation phase of the Regulation (EU) 2021/2282 on health technology assessment will start, managed by the Member State Coordination Group on HTA (HTACG) and all oncology medicines and advanced therapy medicinal products (cell, gene or tissue-based therapies) will be assessed with European JCAs. From 2028, JCAs will be performed for orphan medicines as well, and by 2030, all new medicines will be subject to JCAs. These JCAs only focus on clinical data, while economic analyses (and decisions regarding reimbursement) will remain at the individual country level. Prior to JCAs being performed, there is a separate scoping phase, where each member state provides input into the PICO criteria relevant to them

[316]. EUnetHTA reported that there were challenges in finding HTA agencies willing to actively participate in JCAs, as the timelines for performing the work had high uncertainty, and there was a lack of clarity around defining the PICO [385].

Austria, Belgium, Ireland, Luxembourg and the Netherlands have created the Beneluxa Initiative on Pharmaceutical Policy with the aim to give patients faster access to innovative medicines [386]. It is unclear whether there is a separate PICO development step in these assessments.

Although collaboration with other agencies may produce efficiencies regarding the HTA resources used, if additional processes such as a scoping phase is added to the Australian system of evaluating medicines, the timeframes for the pre-assessment phase would increase.

Faster access to medicines in general

Scotland have introduced a streamlined process for medicine assessment, which was introduced as an interim measure during the COVID-19 pandemic [48]. They created a New Drugs Committee (NDC) to assess the clinical and economic evidence presented by the sponsor, supplemented with comments from a clinical expert. This committee provides advice to the sponsor, so that they may address areas of uncertainty prior to submitting to the Scottish Medicines Consortium (SMC), or if the case is robust, the NDC will support, and the SMC executive will review the medicine rather than requiring review by the whole SMC. These strategies are to reduce the demand on the SMC. It is unclear whether this change in process would alter the development of the PICO criteria.

In Canada, prior to October 2022, CADTH would conduct a systematic review as part of the appraisal of new medicines. However, a recent change that has occurred, is that the pharmaceutical companies now prepare their own submissions. This has placed the responsibility of developing and justifying the PICO criteria onto sponsors [49]. CADTH still develops the PICO and carries out the evaluation for non-sponsored reimbursement submissions [181].

In Germany, a law reforming the pharmaceutical market (Arneizmittelmarkt-Neuordnungsgesetz; AMNOG) was introduced in 2011, requiring the G-BA to perform an early benefit assessment as a basis for reimbursement price negotiations. However, sponsors may set their own price for the first 6 months after marketing authorising, and the assessment of additional benefit of the medicine occurs after initiation of reimbursement. As part of this process, the population for reimbursement must be identical to the indication approved for market authorisation[301].

Faster access to innovative technologies

Many jurisdictions have recently introduced reforms so that innovative treatments for areas of unmet need can be used by patients much faster than traditional approval and reimbursement processes would allow.

Regulatory agencies such as the USA Food and Drug Administration (FDA) and Australian Therapeutic Goods Administration (TGA) have introduced accelerated approval pathways for areas of unmet clinical need, where market approval is provided prior to the clinical benefit for patient-relevant outcomes being confirmed. Generally medicines approved through these pathways have a confirmatory trial pending, although the results are often provided later than expected [387]. Decisions are usually made based on surrogate outcomes. Earlier regulatory approval results in earlier submissions for reimbursement, leading to a much greater level of uncertainty regarding how the treatments affect clinical outcomes.

Australia has a Managed Access Program which allows PBAC to list products for conditions with high unmet clinical need, on terms that allow for resolution of the clinical or economic uncertainties [388]. The guidance around the PICO criteria are identical to standard PBAC submissions. The MSAC also make pragmatic decisions around new technologies such as cell therapies, recommending funding for promising treatments where there is a high level of uncertainty, with the agreement that the sponsors collect real world data on the costs and outcomes of patients treated in Australia (pay-for-performance) [290].

In England, the Cancer Drugs Fund was introduced in 2016, and the Innovative Medicines Fund was introduced in 2022 for non-cancer medicines [389, 390]. These funds allow early access to promising treatments where further data are still required for NICE to make a final recommendation, such as cell and gene therapies. NHS England and NICE then work in partnership with sponsors to address the uncertainty, such as collecting data during a managed access program. The process of scoping the review and developing the PICO criteria remain the same, although occur at an earlier time point [27]. The medicines reviewed under these schemes are reviewed after a predetermined period, after which time a recommendation is made.

In the Netherlands, a new process was developed for conditional inclusion of orphan medicines, known as ‘conditionals’ and ‘exceptionals’ in basic health care. If there is an area of unmet clinical need, the sponsors could request to have their medicine receive conditional reimbursement, while they collect trial data. The trial needs to be completed as rapidly as possibly (within 7 years unless given specific exemption, in which case, no longer than 14 years). In 2019, EUR24.2 million was made available for conditional inclusion of these medicines. Once this ceiling was reached, new applications were added to a waiting list. The procedure of conditional inclusion is recommended to be reviewed every 2 years [300]. This new policy was created for rare diseases, where it can be difficult and time consuming to generate evidence to establish the clinical effectiveness of a medicine. The conditional approval policy was created so that patients with an unmet clinical need can access treatment earlier, if they are eligible, based on the registered indication.

Since July 2021, HAS in France has granted early access to innovative medicines which are presumed safe and efficacious. The medicine must be a novel treatment likely to

offer patients a substantial benefit, there must be a suitable research underway, clinical findings support a presumptive benefit in the context of the existing therapeutic strategy, and the treatment must meet an unmet or insufficiently met medical need [53]. It is unclear whether HAS has any role in defining what outcomes should be collected.

Collection of Real-World Evidence

With market access and conditional reimbursement decisions being made based on early indications of technologies being effective, but where significant uncertainties still exist, real world evidence is being used to address this evidence-gap.

In 2019, Germany introduced the "Law for More Safety in the Supply of Medicines (GSAV)" requiring real world evidence to be collected for all medicines with conditional approval (as a consequence of missing evidence) or for orphan medicines [301, 391]. This allows the G-BA to require pharmaceutical companies to collect routine practice data for the purposes of informing the benefit assessment. In this process, the HTA group IQWiG are required to: 1) inform G-BA if there is a registry available which could be used to collect the data, 2) comment on the quality of the registry; and 3) specify what outcomes data should collected to inform the benefit assessment. The pharmaceutical company, in collaboration with the patient registry, is then required to collect the data. Note, the sponsors are only required to collect data on patients who receive their intervention, not on alternative therapies.

On a related theme, the CADTH post-market drug evaluation (PMDE) program was launched in September 2022 [392]. In order to facilitate the collection of post-market data, CADTH and Health Canada are part of a "RWE steering committee", which are creating a national directory of disease registries [392].

A significant limitation of real-world data collection is the absence of a control arm. Single arm data collection provides further certainty on the risk/benefit profile of the medicine, but not on the incremental effectiveness of the treatment, compared to what would have occurred in the absence of the intervention. This is discussed further in Paper 4.

Reduction of expenditure

In Germany, a new Financial Stabilization Act came into effect in November 2022 to reduce pharmaceutical expenditure. As well as changing the time period that the sponsor can set the price (from 12 months to 6 months) (which does not alter the pre-assessment process), there is also a change in the sales threshold (from EUR50 million/year to EUR30 million/year) beyond which orphan medicines are required to undergo the full AMNOG process, rather than the abbreviated AMNOG process. If the revenue stays below the set threshold, the G-BA deems the "additional benefit" to have been established through market authorisation, and instead focuses on determining the extent of the benefit [375, 393].

ASSESSMENT OF VACCINES

It is accepted that vaccination against disease generates value beyond the elements frequently considered within technology assessments and by decision-makers. Both the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the WHO have published guidelines on the economic evaluation of vaccines for HTA and public funding decisions. These guidelines support the inclusion of broader measures of value [182, 394].

POLICIES AND PROCESSES FOR DETERMINING THE PICO

With respect to the process of developing the PICO for vaccines, the following were considered:

- Is there a separate process for determining the PICO?
- Is there any mandatory pre-submission advice/consultation about the PICO?
- Is the PICO developed by the applicant/sponsor?

Table 29 Policies and processes for developing the PICO for vaccines

Country	Organisation	Separate process	Pre-submission advice	Developed by applicant/sponsor
Australia	ATAGI / PBAC	●	●	●
United Kingdom	JCVI	●	●	○
Europe	EUnetHTA	N/A	N/A	N/A
France	HAS / CTV	●	●	◑
Germany	STIKO	○	○	●
The Netherlands	CoV	○	○	●
Canada	NACI	●	○	●
United States	CDC ACIP	●	●	●
South Korea	KACIP	●	○	○
Taiwan	CDC ACIP	○	○	○

ACIP = Advisory Committee on Immunization Practices; ATAGI = Australian Technical Advisory Group on Immunisation; CDC = Centers for Disease Control and Prevention (in USA) and Centres for Disease Control (in Taiwan); CoV = Committee on Vaccinations; CTV = Technical Vaccination Committee (Comité Technique des Vaccinations) of the HAS; HAS = Haute Autorité de santé; JCVI = Joint Committee on Vaccination and Immunisation; KACIP = Korean Advisory Committee on Immunization Practices; NACI = National Advisory Committee on Immunization; PBAC = Pharmaceutical Benefits Advisory Committee; STIKO = Standing Committee on Vaccination

● Yes ◑ Partial ● No ○ Not reported/No information found

Australia

The Australian Technical Advisory Group on Immunisation (ATAGI) advises the Minister for Health and Aged Care on vaccines suitable for the National Immunisation Program (NIP) and other immunisation issues. Their role includes providing industry sponsors with pre-submission advice on demonstrating vaccine effectiveness and potential use in Australia. This advice, in turn, is used to inform submissions for vaccine funding for PBAC consideration. Following a review of immunisation policy structure and price setting mechanisms in 2005, ATAGI took on the role of advising the PBAC on the clinical effectiveness of vaccines to inform PBAC decision-making about the cost-effectiveness of vaccines.

A sponsor can seek funding of a vaccine on the NIP Schedule and/or through listing on the PBS. The NIP aims to increase national immunisation coverage to help reduce diseases that can be prevented by vaccination. It provides free essential vaccines to eligible people. If NIP funding is sought, a preliminary meeting with the Department is available to sponsors prior to lodging a request for ATAGI advice, to ensure that the proposed vaccine is suitable. The advice requested is focused on the epidemiological data and clinical evidence supporting the proposed clinical claim in each target population for the vaccine and its comparator(s), in particular any assumptions or areas of uncertainty [189]. The application for advice from ATAGI includes a summary of the proposed population, intervention, comparator, key effectiveness and safety outcome(s) (i.e., the PICO elements), and the overall clinical claim for the proposed vaccine [189]. A Vaccine Evaluation Group (VEG) prepares the draft ATAGI advice in consultation with two discussants (assigned by Department) and the ATAGI chairperson. One discussant should have vaccinology expertise, and one should have clinical and/or vaccine program management expertise. They may also obtain additional information from the sponsors if required. The ATAGI discussants and sponsor review the draft advice and provide feedback to the VEG. The draft advice is updated to reflect this feedback and the document is sent to ATAGI for the meeting. ATAGI provides advice to the sponsor and PBAC on the appropriateness of the PICO criteria, clinical algorithm, and any predicted implementation issues [189]. ATAGI meet to consider and determine their advice. Following the meeting the ratified advice document is sent to the sponsor and the PBAC. If the sponsor decides to proceed with the submission after receiving advice from ATAGI, the vaccine submission is lodged with the PBAC approximately 9 weeks after the ATAGI meeting. The PBAC can also request post-submission advice from ATAGI prior to the PBAC meeting to address any matters raised by PBAC HTA evaluation groups, PBAC and the Department which could include elements of the PICO [395]. ATAGI advice may be updated if a resubmission is made to the PBAC as the resubmission could include changes to elements of the PICO [369].

The TGA-PBAC parallel evaluation process also applies to Category 1 and 2 vaccine submissions[34]. A vaccine submission to PBAC is considered at any time from lodgement of the TGA registration dossier. The vaccine submission to PBAC for NIP funding must include the advice from ATAGI and must address any issues raised by ATAGI prior to lodgement of the PBAC submission. These issues could include amendments to the PICO.

A summary of the process is shown in Figure 26.

[34] Category 1 submissions involve a request for PBS or NIP listing of one or more of the following: a first in class medicine or vaccine, and/or a medicine or vaccine for a new population, or a drug with a codependent technology that requires an integrated submission to the PBAC and MSAC or a drug or vaccine with a TGA provisional determination related to the proposed population.
Category 2 submissions relate to a request for PBS or NIP listing of a new medicine or new vaccine, a new indication of a currently listed medicine or vaccine, or to make material changes to a currently listed indication and do not meet the criteria for a Category 1 submission.

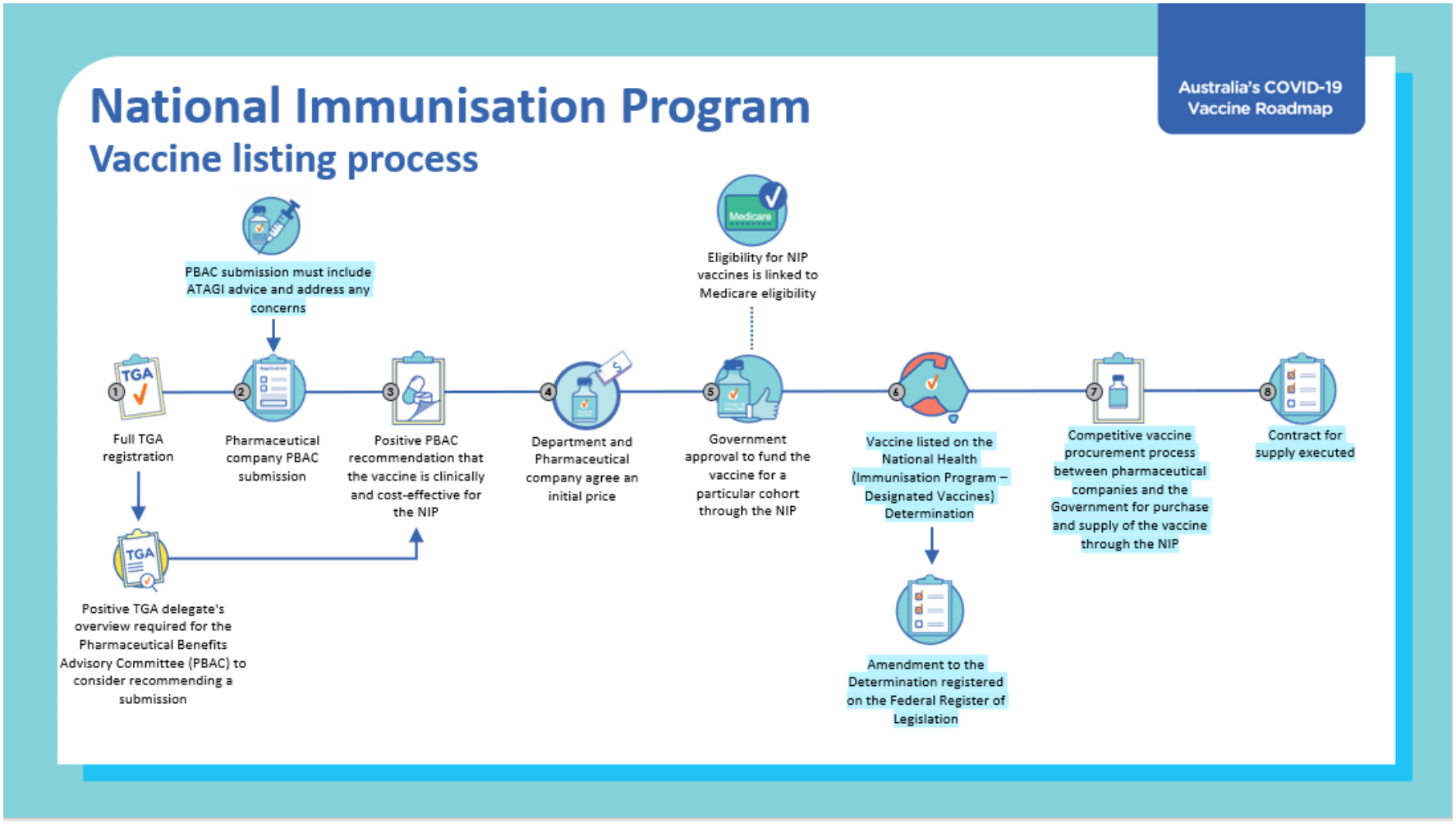

Figure 26 Process of assessment of vaccines for the NIP in Australia

Source: Immunisation Branch, Australian Department of Health and Aged Care

United Kingdom

In the UK, the assessment of vaccines is carried out by the Joint Committee on Vaccination and Immunisation (JCVI), an independent expert committee. The JCVI advises government health and social care departments in the UK and the devolved nations (Northern Ireland, Scotland and Wales). The JCVI consider evidence on the burden of disease, vaccine efficacy and safety and the impact and cost effectiveness of immunisation strategies. They also consider factors for effective implementation strategies.

No information was available for the JCVI regarding development of the PICO. It is likely that a PICO is developed to guide a systematic review of the evidence in line with NICE health technology appraisal methodology guidance [27]. It was not stated how the PICO is developed, who develops the PICO (committee members, evaluation group or sponsor) or if there is a formal scoping process to aid development of a PICO as carried out by NICE for assessment of medicines and therapeutic vaccines [27].

Topics for consideration by JCVI are identified by the UK Health Security Agency (UKHSA; the executive agency for public health that replaced Public Health England) or the health and social care government departments in the UK and the devolved nations following requests for advice by JCVI members, health professionals, the public or through JCVI's annual horizon scanning of vaccines in development. The JCVI assesses preventative vaccines, while therapeutic vaccines are evaluated by NICE. JCVI uses the methodology and criteria of NICE to assess the clinical and cost effectiveness of vaccines. Their advice and recommendations are based on appraisal of the best available evidence drawn from multiple sources, including published and unpublished data, advice from international and national bodies, commissioned research and analyses (e.g., clinical, epidemiological, operational, attitudinal, impact and economic evidence).

Europe (as a single jurisdiction)

Although the organisation and delivery of health services are the responsibility of the European Member States, the EU recognises that there are cross-border threats to health and has initiated the EU Joint Action on Vaccination to strengthen collaboration between Member states, envisioning a Region free from vaccine-preventable diseases [396]. One of the actions on the World Health Organization (WHO) European Immunisation Agenda 2030 (EIA2030) is to engage with National Immunization Technical Advisory Groups (NITAGs), encouraging them to update their national immunisation schedules, and to advise them what evidence is available and what research should be performed. Another action of EIA2030 is to perform HTAs of innovative technologies to advocate for their use in NIPs [396]. JCAs for vaccines will be performed from 2030 onwards.

European countries

In the Netherlands, vaccines may either be reimbursed through the Dutch Drugs Reimbursement System or through the National Immunisation Program [204]. The process for reimbursement through the Drugs Reimbursement System is initiated by the sponsor, and the process is the same as for medicines. The process of including a vaccine on the National Immunisation Program is initiated by the Ministry of Health (which performs horizon scanning twice a year) rather than the sponsor. The Dutch Health Council (*Gezondheidsraad; GR*) and the National Health Care Institute *(Zorginstituut Nederlands;* ZIN) conduct parallel assessments, the GR advising on the optimal strategy of vaccination at the population level, while ZIN advise on whether vaccines should be included in the insurance package for specific at-risk groups. It is unclear how the PICO are developed for these vaccine assessments, or what stakeholder engagement occurs. Formal early scientific advice is available from ZIN.

In France, the Technical Vaccination Committee (*Comité Technique des Vaccinations [CTV])* within HAS provides recommendation regarding inclusion of vaccines on the NIP. The process of developing the PICO and dossier submission can be the same as for medicines (the sponsor initiates the assessment and develops the submission), but there is also the ability for the Minister of Health and approved patient associations, national colleges or learned societies to put in applications for vaccines to be considered [195]. Sponsors may receive early advice and may also have informal dialogue with the CTV when developing their submission [195]. No guidance specific to developing PICO for vaccines submissions was identified.

In Germany, the assessment of vaccines is initiated by the Standing Committee on Vaccination (*Ständige Impfkommission* [STIKO]), based on the burden of disease, medical need, availability of a licensed vaccine and vaccine profile [195]. Working groups develop the PICO criteria, and the systematic review is then performed by the Executive Secretariat at the Robert Koch Institute or contracted out to external experts, with experience in following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [397]. No formal scientific advice for vaccines is available in Germany.

United States of America (USA)

In the USA, recommendations on vaccinations are made by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). They create Working Groups to review the relevant published and unpublished data on the clinical need for vaccines, and the effectiveness of vaccines for specific disease areas. The Working Groups follow GRADE evidence-based medicine practices for assessing vaccines versus alternative strategies (e.g. vaccination vs no vaccination), the first step of which involves defining the PICO of interest [398]. This is done prior to the assessment, but there is no formal process for seeking stakeholder input (beyond the Working Group membership).

Canada

Federal vaccination program recommendations are made by the National Advisory Committee on Immunization (NACI) in Canada. NACI provides the Public Health Agency of Canada (PHAC) with evidence-based medical, scientific, and public health advice relating to use of vaccines to prevent infection and disease, as well as for certain prophylactic agents such as immunoglobulins. The terms of reference state that NACI advice to PHAC considers the information required by both public health decision makers and health care providers. NACI recommendations supplement regulatory decisions based on disease burden and public health needs in Canada and therefore the Committee is not restricted by the approved vaccine indication. NACI can make "off-label" recommendations when supported by a public health ethics analysis [399].

From 2019, PHAC has expanded the mandate of NACI to include the consideration of programmatic factors, in addition to burden of disease and vaccine characteristics, when developing evidence-based recommendations. This is undertaken to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels. NACI has also developed an Ethics, Equity, Feasibility, and Acceptability (EEFA) Framework, which provides a mechanism for decision-makers to systematically consider these four factors, alongside effectiveness and cost-effectiveness, when making recommendations about vaccination programs [96]. The guidance currently employed by NACI includes 8 decision-criteria (i) burden of disease, (ii) vaccine characteristics (e.g., efficacy, safety), (iii) research questions, (iv) immunisation strategy and program, (v) cost-effectiveness, (vi) ethical considerations, (vii) equity, (viii) feasibility, (viii) acceptability [400].

Economic evaluation of vaccines is included in the assessment process. Defining the decision problem to be addressed by the economic analysis and the selection of PICO elements to determine selection of clinical evidence of vaccine effectiveness are presented in the guidelines [400]. The guidelines recommend two reference case analyses for the economic evaluation of vaccination programs: one carried out from a publicly funded health system perspective and the other from a societal perspective. The societal perspective should include the full range of impacts associated with vaccination programs. Additionally, multiple sensitivity analyses are also recommended. The aim is to provide NACI decision makers with a more comprehensive overview of the impacts of a vaccination program.

South Korea

The Korea Advisory Committee on Immunization Practices (KACIP) is a NITAG serving the Republic of Korea that meets at least twice per year [200, 401]. This committee advises the Ministry of Health and Welfare (MoHW) and is involved in the decision-making process for the introduction of new vaccines onto the National Immunization Program (NIP). The terms of reference for KACIP are to:

- designate diseases to be targeted for immunization and remove diseases from the list, as needed
- develop plans for the control of vaccine preventable diseases
- develop practical guidelines and policies for immunization

The Committee provides advice to both the public and private healthcare sectors but only the public sector is mandated to follow all KACIP recommendations approved by the MoHW [401].

When a decision has been made to add a topic to the KACIP meeting agenda, the Korea Disease Control and Prevention Agency (KCDC) requests the appropriate subcommittee to review all relevant data, gather the opinions of experts, and suggest a policy recommendation. If no sub-committee or advisory committee yet exists that can address the topic, the KACIP requests the KCDC to gather relevant data for their review. There was no information on whether a PICO was developed to guide collection of evidence or if a PICO is developed, who determines the PICO elements (the KACIP or a subcommittee). Evidence assessed includes published and unpublished data on the disease burden in Korea (including clinical characteristics of the disease, and incidence, mortality, and case fatality rates), data on efficacy, effectiveness, and safety of the vaccine, and economic data on the disease and vaccine, including the vaccine's cost-effectiveness (in terms of cost/QALY) and financial impact of implementing the new vaccine program.

The Korea Food & Drug Administration (KFDA), which was responsible for licensing the vaccine in Korea may be asked to provide information on the vaccine's immunogenicity in the local population, safety profile, and clinical trial results. Information on the availability of a vaccine supply and sources of the vaccine and WHO recommendations are also considered. Economic data is often prepared with help from a local economist or expert in preventive medicine. Since the economic and disease burden parameters change from country to country, data from Korea are always preferred, and local studies are sometimes recommended although global economic data from WHO or from other countries are often used as a reference. Economic evaluations conducted by vaccine producers are not considered because of the potential for bias. Various factors and types of data (e.g., disease burden vs. vaccine cost-effectiveness) are not ranked in order of importance by the KACIP or subcommittees when making recommendations.

Once the sub-committee reviews the epidemiological, vaccine, and economic data, members try to reach a consensus on recommendations concerning control measures for the disease in question; this includes immunisation. If the sub-committee cannot reach a consensus, the Chairperson decides what recommendations to give to the KACIP. The KACIP members discuss each issue in depth and develop recommendations, usually by consensus. While most decisions made by the Committee are approved by the MoHW and implemented, KACIP recommendations are not legally binding; occasionally recommendations have not been implemented for some time due to a lack of funding or the need to revise laws before enacting the policy change [401].

Taiwan

In Taiwan, the Advisory Committee on Immunisation Practices (ACIP) meets quarterly to review current national immunisation policies. The ACIP has 19 members with backgrounds including public health, epidemiology, paediatrics, immunology, education and nursing. Members of the ACIP also represent different bureaus in the Department of Health concerned with immunisation as well as local health departments. Vaccines considered by the ACIP are subsequently ranked and prioritised for adoption on the NIP [402]. The Centre for Disease Control (CDC) submits a list of new and underutilised vaccines for the ACIP to assess based on benefits and costs. It was not possible to determine if a PICO is developed during the evaluation. The methods that ACIP use in the pre-assessment phase were not publicly available.

INVOLVEMENT OF STAKEHOLDERS IN THE DEVELOPMENT OF THE PICO

A summary of stakeholder involvement for the development of PICO for vaccine assessments is shown in Table 30. The table summarises responses to the following question:

Is there any involvement of clinicians (HCPs (Health Care Professional)), sponsors/industry, public, patients, regulatory agencies or other advisory bodies in determining PICO?

Table 30 Stakeholder involvement in the development of the PICO for vaccines

Country	Organisation	HCPs	Sponsors/ industry	Public	Patient groups	Regulatory agencies	Other advisory bodies
Australia	ATAGI/ PBAC	●	●	◑	●	●	●
United Kingdom	JCVI	○	○	○	○	○	○
France	HAS/CTV	○	◑	○	○	○	○
Germany	STIKO	●	●	●	●	○	●
The Netherlands	CoV	○	◑	○	○	○	○
United States	CDC ACIP	○	◑	●	●	○	●
Canada	NACI	○	●	○	○	○	○
South Korea	KACIP	○	○	○	○	○	○
Taiwan	CDC ACIP	○	○	○	○	○	○

ACIP = Advisory Committee on Immunization Practices; ATAGI = Australian Technical Advisory Group on Immunisation; CDC = Centers for Disease Control and Prevention (in USA) and Centres for Disease Control (in Taiwan); CoV = Committee on Vaccinations; CTV = Technical Vaccination Committee (Comité Technique des Vaccinations) of the HAS; HAS = Haute Autorité

de santé; HCP = health care practitioners; JCVI = Joint Committee on Vaccination and Immunisation; KACIP = Korean Advisory Committee on Immunization Practices; NACI = National Advisory Committee on Immunization; PBAC = Pharmaceutical Benefits Advisory Committee; STIKO = Standing Committee on Vaccination

● Yes ◑ Partial ● No ○ Not reported/No information found

Australia

Prior to the vaccine submission to the PBAC, some stakeholders are able to have input into elements of the PICO during the drafting of the ATAGI advice and during the ATAGI meeting [369].

Pre-submission advice from ATAGI includes consideration of the PICO criteria [369]. Sponsors can request a preliminary meeting with members of the Department prior to submitting a formal request for ATAGI advice to discuss elements of uncertainty including the PICO [369]. Once the sponsor has submitted the application for ATAGI advice prior to the PBAC submission, two expert discussants (assigned by the ATAGI chairperson) and the sponsor (if requested) are able to provide advice and additional information to the VEG including about elements of the PICO.

The VEG will assess the advice request, confirming if the PICO elements and clinical algorithm are appropriate or not, answer questions from the sponsor, and highlight any areas of uncertainty for ATAGI consideration. ATAGI focus on aspects that affect the sponsor's PBAC submission including the appropriateness of the intended population, relevant comparators, specific and relevant outcomes, and the applicability of evidence to the intended use in Australia. Sponsors can ask ATAGI specific questions which will be addressed by the VEG and ATAGI.

The ATAGI holds a face-to-face or online meeting to consider and determine their advice. ATAGI membership includes health care professionals, infectious disease experts, public health experts and a member of the Consumer Health Forum [403]. Occasionally specialists in a particular field may also be co-opted onto ATAGI on an as-needed basis. This may occur when issues arising in relation to a particular vaccine require specialist advice outside of the expertise of ATAGI's membership. Additionally, the ATAGI discussants lead the conversation about the advice at the ATAGI meeting, targeting the areas of greatest uncertainty, where disagreement is possible, or where specific technical advice is required.

There are additional opportunities for stakeholder input when the vaccine submission is lodged for PBAC assessment. As for medicines, stakeholder comments are available with the submission for consideration by the PBAC evaluation group or are considered at the PBAC meeting. Issues raised by individuals (deidentified) are summarised and the complete summary of comments from groups or organisations are provided to the PBAC and the applicant. Although at this point the PICO has already been developed and discussed at the ATAGI meeting, comments for PBAC consideration can inform the evaluation or the deliberations of the PBAC when considering if the PICO elements are appropriate. PBAC can seek further information from stakeholders where uncertainties

remain (usually from relevant representative organisations). Stakeholder comments are included in the PBAC Public Summary Document (PSD).

United Kingdom

Stakeholders beyond the committee are not directly involved in the PICO development process but their provision of information/evidence during the evaluation of the vaccine submission can potentially impact on the JCVI's endorsement of the PICO elements. Stakeholder involvement during the evaluation includes:

- committee members will normally include individuals from academia, practising clinicians who have expertise in one or more relevant areas and at least one (but preferably two) lay members who provide the committee with a wider lay perspective on immunisation issues.
- several designated representatives ("observers") of government departments and health or public health bodies routinely attend Committee meetings and may also attend Sub-committee meetings. "Observers" have access to most of the Committee papers and if directed by the Chair may contribute to the Committee discussions to, for example, clarify points of fact, provide additional information or offer an interpretation of data. They are not able to vote.
- other organisations and individuals may be invited to meetings by exception, for example, to present data to the Committee and may be provided with relevant papers as appropriate.
- unpublished data on the safety, immunogenicity and efficacy of vaccines can be provided by the sponsors or academic research groups
- commissioned research and analyses from external bodies/research groups (e.g., clinical, epidemiological, operational, attitudinal, impact and economic evidence).
- advice from international and national bodies (e.g., WHO, ACIP, International Organisation for Migration, NICE, professional bodies, patient groups, charities)
- correspondence with key experts
- public calls for evidence or unpublished data from interested parties. Specific groups/organisations believed to have an interest in the call for evidence will be notified although the call is open to any group/organisation with an interest in the issue.

After reaching a decision on the issue under consideration, JCVI may issue an interim statement allowing for a short (approximately 1 month) consultation period with stakeholders that have submitted evidence to inform the Committees decision before the Committee reaches a final position and makes a final statement that is subsequently published [207].

European countries

For the evaluation of vaccines in Germany, STIKO working groups develop the PICO criteria, and all members of STIKO are given the opportunity to comment on the PICO. STIKO comprises of experts in a range of fields including paediatrics, family medicine, virology, immunology, epidemiology, public health and evidence-based medicine. Working groups comprise of 2 to 4 members of STIKO, 1 to 2 members of the Executive Secretariat in charge of organisational and scientific matters, and external experts appointed by the working group as needed. It is unclear whether manufacturers of vaccines are given any opportunity to provide input. The Standing Operating Procedures do not describe any public or patient input into the PICO [397].

In France, early HTA advice (with HAS) can be provided for vaccines addressing diseases with an unmet (or poorly met) clinical need, innovative vaccines (a new mode of action), and where Phase 2 trials are already available [195].

Likewise in the Netherlands, early advice with ZIN is possible [195], although it is unclear who the advice is provided to. No guidance was found specifically on developing the PICO criteria for vaccines in the Netherlands or France, or which stakeholders are involved.

United States of America

No information about stakeholder engagement at the PICO development stage was identified. At least one member of the ACIP must be an expert in the consumer perspective and/or social and community aspects of immunisation programs, and ACIP meetings are open to the public. Sponsors may be asked to present to the work group, or to answer questions [404].

Canada

No information was identified on stakeholder input into development of the PICO criteria for vaccines assessed by NACI. NACI does include stakeholders that are involved in vaccine evaluation and therefore may have an impact on the consideration of the PICO elements by the Committee.

NACI is composed of 16 volunteer members with expertise, knowledge and experience in: immunisation; public health; prevention of vaccine-preventable diseases; previous experience on vaccine advisory committees or with paediatric or adult infectious diseases; geriatrics; allergy/immunology; and other health related fields, such as nursing, pharmacoeconomics, social sciences, epidemiology and infectious-disease modelling. The Committee aims to reflect the diversity and demographics of Canada in such areas as, gender, official language, race, and ethnicity to help ensure a balance of perspectives. Other participants supporting the work of NACI but without voting status include ex-officio representatives (other government organisations) and

representatives of national or professional associations or committees. PHAC may also invite certain individuals who are not members of the advisory body or participating representatives to provide input on a specific topic or agenda item or speak to NACI on a given topic/agenda item or an individual may ask to observe all or part of a meeting [399].

South Korea

No information was identified on stakeholder involvement in developing PICO criteria for vaccine evaluation by KACIP in Korea.

The KACIP consists of about 15 members including a chairperson and specialists in internal medicine, paediatrics, obstetrics, microbiology, preventive medicine, and nursing, drawn from affiliated organisations. The Committee also includes a representative from a consumer group, the Director of Disease Prevention at the Korea Centers for Disease Control and Prevention (KCDC), and the Director of Biologics at the Korea Food and Drug Administration (KFDA). The KACIP has sub-committees that are working groups gathering, analysing, presenting information and making recommendations on specific topics to inform Committee decision-making. Subcommittees usually have <20 members, including some KACIP members, representatives of the affiliated organisations (medical, academic, nursing and consumer organisations in Korea) and from academia, as well as other external experts. As with the KACIP, representatives from vaccine companies are not allowed to be members of subcommittees.

The KACIP meetings are open to the public. Individuals/organisations wishing to attend a meeting as observers, such as vaccine producers, members of civil organizations or academia, must apply in writing to obtain permission to attend. However, the Chairperson can hold the meeting in private, if particularly sensitive or controversial topics are being discussed.

Taiwan

No information was identified on which stakeholders provide input into the pre-assessment phase for vaccines evaluated by ACIP. The ACIP committee consists predominantly of clinicians with a public health background, and some are members of the Taiwan Immunization Vision and Strategy [402].

CONSIDERATIONS FOR DETERMINING POPULATION(S)

With respect to the target population selected for inclusion in the PICO for assessment of vaccines, the following were considered:

- Is any advice/guidance provided?
- Does the population have to match the pivotal trial?

- Is the (proposed) registered indication considered?
- Can the reimbursed indication be different to the (proposed) registered indication?
- Does guidance around PICO explicitly require consideration of population subgroups?
- Are equity considerations regarding Population mentioned?

Table 31 Guidance, policies and conventions for determining the target population for vaccines

Country	Organisation	Guidance	Pivotal trial	Registered indication	Reimbursed indication	Guidance around subgroups	Equity
Australia	ATAGI / PBAC	●	◑	●	●	●	●
United Kingdom	JVCI	●	○	○	○	○	○
France	HAS / CTV	◑	○	○	○	◑	○
Germany	STIKO	●	●	○	○	●	●
The Netherlands	CoV	◑	●	○	○	◑	●
United States	CDC ACIP	●	○	○	○	●	●
Canada	NACI	●	●	○	○	○	●
South Korea	KACIP	●	○	○	○	○	○
Taiwan	CDC ACIP	●	○	○	○	○	○

ACIP = Advisory Committee on Immunization Practices; ATAGI = Australian Technical Advisory Group on Immunisation; CDC = Centers for Disease Control and Prevention (in USA) and Centres for Disease Control (in Taiwan); CoV = Committee on Vaccinations; CTV = Technical Vaccination Committee (Comité Technique des Vaccinations) of the HAS; HAS = Haute Autorité de santé; JCVI = Joint Committee on Vaccination and Immunisation; KACIP = Korean Advisory Committee on Immunization Practices; NACI = National Advisory Committee on Immunization; PBAC = Pharmaceutical Benefits Advisory Committee; STIKO = Standing Committee on Vaccination

● Yes ◑ Partial ● No ○ Not reported/No information found

Australia

For vaccines, ATAGI considers the sponsor's choice of population, taking into account the disease incidence/burden of disease, and whether any high-risk groups are adequately described. If the vaccine is proposed for use in a subgroup(s) of the Australian population with the disease or condition, sponsors need to indicate whether the usual course of the disease or condition – or the available treatment options for that subgroup(s) – differs from that of the whole population. If relevant, they also consider whether one of the subgroups should be a catch-up population (i.e. if a proposed new indication is given at a certain age, should the vaccine also be made available to those older than the specified age) [369]. The rationale for listing the vaccine should also describe any impacts on issues such as access or equity, and the sponsor

should consider whether the disease incidence is likely to differ in Indigenous Australians.

United Kingdom

No guidance on population selection was identified for vaccine assessment by the JCVI. As JCVI follows NICE methods for economic evaluation of vaccines, the methodological guidance for population selection is the same as for medicines [27].

European countries

In France, HAS has produced guidelines on developing economic evaluations, which state that the analysis population should include both those whose health is directly impacted by the intervention (i.e. vaccinated population) as well as those impacted indirectly (general population and caregivers), although the base case is restricted to those directly affected [405]. Subpopulations may be relevant to include if variability is expected in regard to the health effects or costs of the intervention (or comparator).

In Germany, STIKO can form a working group and start the assessment process prior to the regulatory approval for vaccines with a high degree of public interest, but their guidance does not state whether the population considered for the NIP should align with the indication that has been approved by the regulator or applied for.

In the Netherlands, no guidance on developing the PICO criteria for vaccines was identified. However, equity is one of the criteria considered when making decisions about whether vaccines should be added to the NIP [204]. Inclusion of vaccinations on the NIP should consider not only the best possible protection of the population as a whole, but also that the benefit should be distributed fairly across the population, with protection provided on the basis of need [406]. If the vaccine is being considered for a certain target group, then the burden of disease for that group needs to be outlined.

United States of America

CDC ACIP working groups define the population of interest to be considered, but their handbook for developing evidence-based recommendations does not provide guidance on this [398]. ACIP's general best practice guidelines for immunisation states that recommendations are influenced by age-specific risks for disease, complications and responses to vaccination, so by implication, subgroups based on age should be assessed [407].

Canada

NACI provide guidelines which were expanded in 2019, and specifically discuss three separate populations: populations intended for the vaccination program, populations at risk for the disease of interest, and populations that may be indirectly affected either

through externalities or spillover effects. The decision problem should include, at minimum, the first study population, and where applicable, the latter two populations. They also suggest exploring equity, through methods such as distributional cost-effectiveness analysis [408]. The new EEFA framework suggests looking at subgroups by age, which can contribute to different disease susceptibility, and by systemic factors such as remoteness or socioeconomic status [96].

South Korea

No guidance on defining the relevant population was identified for assessment of vaccines by the KACIP.

Taiwan

No guidance on defining the target populations for vaccines in Taiwan was identified.

CONSIDERATIONS FOR DETERMINING COMPARATOR(S)

With respect to selection of comparator(s), the following were considered:

- Is there explicit advice (guidance) on comparator selection? E.g., should it be the most cost-effective? Most used?
- Is the comparator defined?
- Is the choice of comparator based on clinical practice?
- Is the choice of comparator based on cost?
- Is the choice of comparator based on prior reimbursement decisions?
- Are multiple comparators used?

Table 32 Guidance, policies and conventions for determining the comparator for vaccines

Country	Organisation	Guidance	Defined	Clinical practice	Based on Cost	Prior reimbursement decisions	Multiple comparators
Australia	ATAGI/ PBAC	●	●	●	●	◑	●
United Kingdom	JCVI	●	●	●	○	○	○
France	HAS/CTV	●	○	○	○	○	○
Germany	STIKO	●	●	○	○	○	○
The Netherlands	CoV	●	○	○	○	○	○
United States	CDC ACIP	○	○	○	○	○	○
Canada	NACI	●	●	●	●	●	●
South Korea	KACIP	●	○	○	○	○	○
Taiwan	CDC ACIP	●	○	○	○	○	○

ACIP = Advisory Committee on Immunization Practices; ATAGI = Australian Technical Advisory Group on Immunisation; CDC = Centers for Disease Control and Prevention (in USA) and Centres for Disease Control (in Taiwan); CoV = Committee on Vaccinations; CTV = Technical Vaccination Committee (Comité Technique des Vaccinations) of the HAS; HAS = Haute Autorité de santé; JCVI = Joint Committee on Vaccination and Immunisation; KACIP = Korean Advisory Committee on Immunization Practices; NACI = National Advisory Committee on Immunization; PBAC = Pharmaceutical Benefits Advisory Committee; STIKO = Standing Committee on Vaccination

● Yes ◑ Partial ● No ○ Not reported/No information found

WHO guidance on the economic evaluation of vaccination states that the comparators under study should be clearly described. The most relevant comparison for new vaccines is usually current practice. Where existing practice appears to be cost-ineffective compared to other available options, other relevant options should be included in the analysis (e.g., best available alternative, a viable low-cost alternative or a do-nothing option). Non-vaccine interventions against the same disease should be considered

where appropriate and should be captured by the current or alternative practice comparators [182].

Australia

In Australia, there is separate guidance for choosing the comparator for a vaccine rather than a medicine, but the content of the guidance is very similar between the two guidance documents [189, 285]. Submissions for a vaccine to go on the NIP should select the comparator based on the current alternative vaccines or therapies used in Australia, and that are most likely to be replaced in clinical practice [189]. Although a single comparator is appropriate in most cases, multiple comparators may be included if there are subgroups (perhaps by age) for whom clinical practice differs. If there is an existing vaccine for the same indication available on the NIP or recommended by the PBAC for use on the NIP, then this is usually the main comparator. Where immunisation for the target population and disease is currently undertaken by the States and Territories, this needs to be discussed, but would not be considered a comparator. Use of 'near market' comparators is encouraged [189]. If no vaccines are currently available for the proposed indication, then the main comparator would usually be standard medical management.

United Kingdom

There was no guidance identified on the selection of appropriate comparators for vaccine assessment but as the JCVI follows the technology appraisal methodology of NICE for their assessment of vaccines they may adapt criteria in the NICE guidance [27]. The Cost-Effectiveness Methodology for Immunisation Programmes and Procurements working group (CEMIPP) recommends that there should be an incremental analysis of all relevant comparators which is considered best practice for cost-effectiveness analysis. The most important comparator is the status quo, but all relevant options need to be described and justified [409, 410].

European countries

No guidance specific to determining the comparator for vaccines was identified for France and the Netherlands.

For vaccine assessment in Germany, a STIKO working group develops the PICO criteria (which includes the 'Comparator' component), but no guidance on selecting the appropriate comparator is provided in their Standard Operating Procedures [397].

United States of America

Very limited guidance on choosing a comparator is provided in the ACIP Handbook for developing evidence-based recommendations [398]. The working group needs to specify the comparator, and the example provided is "another vaccine".

Canada

NACI state that for the evaluation of vaccination programs, all current interventions should be considered, any near-market comparators, and those that may be displaced by the proposed vaccine being evaluated. All relevant comparators should be included (there is usually more than one). Comparators could include:

- other existing preventive vaccines (alternative vaccines for the same pathogen, vaccines with additional valency, or different implementation or delivery of the same vaccine, such as universal versus targeted vaccination),
- screening programs (such as for human papillomavirus),
- preventive medication-based interventions (such as preventive medicine for malaria, prophylaxis for human immunodeficiency virus),
- preventive non-medical interventions (for example, physical barriers such as face masks to reduce the spread of respiratory infections, or condoms for sexually transmitted diseases, or behaviour modifications such as social distancing, hand washing, and lock downs), and
- current treatment approaches including best supportive care [408].

South Korea

No guidance on defining the comparator was identified for assessment of vaccines by the KACIP.

Taiwan

No guidance on determining the appropriate comparator was identified for Taiwan.

CONSIDERATIONS FOR DETERMINING OUTCOMES

When determining health outcomes of interest, is there guidance on:

- appropriate outcomes?
- use of Patient Reported Outcome Measures (PROMs)?
- surrogate outcomes (without translation)?
- outcomes beyond the treated individual?
- non-health outcomes?

The summary of how jurisdictions approached outcome measures for vaccines was grouped by topic, rather than by jurisdiction, for ease of reading. However, Table 33 summarises what was found on outcome measurement for vaccines in the guidance documents from NITAGs and the associated agencies in the different jurisdictions considered.

Table 33 Guidance, policies and conventions for determining the outcomes for vaccines

Country	Organisation	Appropriate outcomes	PROMs	Surrogate outcomes	Beyond the treated individual	Non-health outcomes
Australia	ATAGI /PBAC	●	●	●	●	●
United Kingdom	JCVI	●	●	●	●	◑
France	HAS / CTV	○	○	○	○	○
Germany	STIKO	◑	●	●	●	●
The Netherlands	CoV	●	●	●	◑	◑
United States	CDC ACIP	◑	○	●	○	○
Canada	NACI	●	●	●	●	●
South Korea	KACIP	○	○	○	○	○
Taiwan	CDC ACIP	○	○	○	○	○

ACIP = Advisory Committee on Immunization Practices; ATAGI = Australian Technical Advisory Group on Immunisation; CDC = Centers for Disease Control and Prevention (in USA) and Centres for Disease Control (in Taiwan); CoV = Committee on Vaccinations; CTV = Technical Vaccination Committee (Comité Technique des Vaccinations) of the HAS; HAS = Haute Autorité de santé; JCVI = Joint Committee on Vaccination and Immunisation; KACIP = Korean Advisory Committee on Immunization Practices; NACI = National Advisory Committee on Immunization; PBAC = Pharmaceutical Benefits Advisory Committee; STIKO = Standing Committee on Vaccination

● Yes ◑ Partial ● No ○ Not reported/No information found

Appropriate outcomes

Many NITAGs and associated organisations that conduct value assessment of vaccines to inform adoption and reimbursement decisions by policymakers, limit their assessments to the health benefits for the vaccinated individual, the costs associated with vaccination, the disease avoided and, in some cases, herd-immunity [213].

In the WHO guidance on the "*Principles and considerations for adding a vaccine to a national immunization programme: from decision to implementation and monitoring*" [411], performance factors that decision-makers should consider include the vaccine's safety profile; efficacy, effectiveness and duration of protection; the age at which it can be administered or is most effective; and added benefits, such as indirect (herd) immunity and cross-protection against other diseases. While data for efficacy demonstrating that the vaccine under assessment can prevent the disease in the target population is required to obtain regulatory approval, effectiveness is the focus of vaccine HTA and describes the protection obtained by implementation of the vaccine program and reflects the performance of the vaccine as delivered to the target population. Vaccine effectiveness is usually lower than vaccine efficacy because of program-related factors (e.g., errors in vaccine storage, preparation or administration

of the vaccine, incomplete coverage or uptake). However, the effectiveness of the vaccine can be greater than expected due to the indirect benefits of vaccination (e.g., herd immunity). Vaccines can also alter the epidemiology of a disease by changing the age pattern of people with the disease or by changing the predominant strains causing the disease ("serotype replacement"). Disease surveillance activities may be required following introduction to monitor the overall impact. Australia establishes monitoring and evaluation plans to determine the vaccination program impact on disease epidemiology. Other aspects of a vaccine's performance that have implications for an immunisation program are the age at which it becomes effective or has maximum effectiveness, and the duration of protection that it provides. Vaccines with waning protection may periodically require repeated doses or booster doses, which must be considered when assessing the costs and feasibility of the vaccination program [411]. This aspect is also assessed in Australia.

The use of broader outcomes to assess the value of vaccination is incorporated into the more recent WHO guidance on economic evaluations of immunization programs that aims to increase standardisation of vaccine economic assessment globally [182]. For example, these guidelines specifically discuss methods to incorporate assessment of equity in addition to efficacy (e.g., through extended-CEA to assess equity and efficiency considerations in parallel, or through distributional-CEA to assess trade-offs between equity and efficiency) [412].

A study by Bell (2022) based on a literature review and Delphi panel of experts, concluded that the broader value elements relevant to vaccines are not consistently considered in the HTA processes of multiple higher income countries [413]. These elements are:

- disease impact on length of life
- disease impact on patient quality of life (QoL)
- disease impact on carer QoL
- burden of disease
- value to other interventions
- reproduction value
- prevention of the development of antimicrobial resistance (AMR)
- social equity
- productivity of patients
- productivity of carers
- costs-offset to healthcare system, and
- macroeconomic effects.

Suggested priority areas for HTA improvement include: more consistent and comprehensive consideration of (1) broader cost offsets within the health care system, (2) impact on carer quality of life, (3) reproduction (R) value, (4) impact on AMR via reduced bacterial transmission, and (5) macroeconomic effects. To achieve a broader recognition of the value of vaccines, the authors recommended a three-pronged

approach including the collection of high-quality evidence, improvement of technical and analytical ability within HTA and infectious disease modelling, and engagement with all stakeholders involved to generate willingness to change.

Similarly, Beck (2022) also concluded that the broad value of vaccines is only partly or inconsistently considered in HTA using CEA. The benefits considered in CEA differed by country e.g., the UK considered benefits from a healthcare payers' perspective that includes indirect health benefits (e.g., from herd immunity) but excluded indirect costs of lost productivity, while Germany, the Netherlands and USA have taken a broader societal perspective that does include indirect productivity costs. Beck et al noted that published frameworks commonly propose expanding currently considered vaccination benefits to include outcome-related and behaviour-related productivity gains, herd immunity, equity, prevention of AMR and macroeconomic impact [412]. Results of these studies are in line with other publications arguing for comprehensive consideration of the narrow and broad effects of vaccines on both health and economic outcomes [182, 394, 412, 414].

Adoption of a broader value assessment framework requires inclusion of broader outcomes in the PICO. Individual outcomes as elements of a broader value framework for vaccines may vary according to the stakeholder perspective. Not all value elements may be relevant or applicable to each vaccine assessment as this may be influenced by the evaluation perspective and economic analysis.

Similar to the assessment of medicines, all HTA groups consider that the assessment of health benefits should include patient-relevant outcomes, such as mortality, morbidity and quality of life.

In Australia, guidance from ATAGI states that the outcomes should include the impact on patient and population health. It should also include access, equity, and nonhealth-related impacts [189].

In the UK, JCVI uses a similar methodology for their economic analysis to NICE to ensure consistency in spending decisions between medicines and vaccines when determining whether a vaccination program is cost-effective. The perspective on outcomes is direct health outcomes (for patients, or when relevant, carers) and the perspective on costs is the NHS and Personal Social Services [207]. JCVI carries out CEA in line with NICE methodology. Societal costs are not included in the CEA. Using the NICE approach, the general consequences for the wider group of patients in the NHS are considered alongside the effects for those patients who may directly benefit from the vaccination program of interest [415]. Most relevant benefits and costs are included in the economic analyses JCVI receives (e.g., herd-immunity and cost-saving to the NHS of vaccination). Where health benefits or costs that could impact the incremental cost-effectiveness ratio (ICER) have not been included in the economic analysis, JCVI may request additional sensitivity analyses or can calculate a quality adjusted life year (QALY) adjustment factor (QAF) or a cost adjustment factor (CAF) to correct the over or under estimation.

In 2016, the Cost-Effectiveness Methodology for Immunisation Programmes and Procurements working group (CEMIPP) for the UK DoH reviewed all aspects of the determination of the cost-effectiveness of a proposed or existing immunisation program based on appropriate epidemiological analysis and modelling [416]. Their report considered that the JCVI should adopt full economic utility as the scope of benefit only if it was adopted by the Appraisal Alignment Working Group (AAWG) and only if implemented as a trial in addition to current analysis [410]. The purpose of the AAWG was to characterise the range of practice across organisations, to understand the reasons for divergence in practice, to consider the possibility of identifying "best practice" where possible, and to make proposals for measures to align practice where appropriate [416]. Following stakeholder consultation and consideration of the CEMIPP report by the AAWG, the UK government also stated that it encouraged further research into "peace of mind" benefits, 'differential weighting', especially in the context of assessing the relative value of the prevention of rare severe illness in children, the appropriate cost-effectiveness threshold, and incorporating the impact of a vaccination program on reducing the use of anti-microbials [417].

In Canada, NACI provides guidance on the outcomes and costs that should be considered during evaluation of a vaccine [400]. They require that the outcome measures should be the same for each comparator considered. They have historically reviewed safety, efficacy, immunogenicity, effectiveness and burden of illness. Recently, PHAC has expanded this mandate to include consideration of programmatic factors—economics, ethics, equity, feasibility and vaccine acceptability—in developing evidence-based recommendations. NACI is continuing to refine its methodological approach to include these programmatic factors. NACI statements will include varying degrees of programmatic analyses for public health programs. The efficacy or effectiveness of vaccines should be determined with comparative studies (either RCTs or observational studies) that report the incidence of the infectious disease targeted by the vaccine, in the vaccinated group versus relevant comparator(s). The primary endpoint of these studies should be defined as clinically apparent infection that meets clinical and laboratory diagnostic criteria. When assessing estimates of vaccine effectiveness, criteria to be considered are vaccine effectiveness by dose and time (e.g., waning protection), pathogen variation-specific effectiveness (i.e., serotypes, serogroups, strains), and geographic and vaccine recipient factors that may affect effectiveness. Indirect effects of a vaccine are captured as population-level effectiveness (herd immunity) which is dependent on the distribution of immunity conferred by the vaccine and natural infection within the population, the transmissibility of the infection, and contact patterns of individuals in the population [400]. Vaccine coverage is an important factor in determining effectiveness at the population-level.

As two reference case analyses (one conducted from the publicly funded health system perspective, and the other conducted from the societal perspective) are presented, broader outcomes (e.g., educational outcomes, productivity-related benefits, equity) and costs consistent with these perspectives need to be included in the PICO to support

these analyses. The societal perspective captures all health outcomes and health system costs from the health system perspective. In addition, it captures impacts that fall outside of the publicly funded health system, including healthcare costs not publicly funded by the health system, direct out-of-pocket costs, losses in productivity, consumption, education, social services and community services, and environment. Longer-term impacts such as the effect of childhood illness on an individual's neurodevelopmental impairment, educational achievement, and subsequent long-term productivity (and consumption) are requested to be considered where relevant and feasible [400]. The NACI guidance on economic evaluation of vaccination programs in Canada includes an impact inventory table containing a list of health and non-health outcomes that could result from vaccination programs to assist with the development of the two reference cases [400].

Guidance from the USA simply states that working groups should choose the important outcomes for every question (benefits, harms), and that these may vary within and across cultures, or when different perspectives are considered (general population, patients, clinicians or policy makers) [398]. Examples of relevant outcomes provided include rates of disease, hospitalisation, death, and adverse events [398].

In Germany, the economic analysis takes into account all endpoints relevant to the respective indication (e.g. disease case, complications, hospitalisation and/or death), as well as the measure of benefit in the form of quality-adjusted life years (QALYs) [418]. Other important outcomes are vaccine-induced protection, degree of protection, duration of vaccine-induced protection, adverse effects of vaccinations at the individual and population level, and indirect effects such as vaccine-induced herd protection, age shifting of incidence caused by vaccination, and serotype replacement.

In the Netherlands, guidance for developing the PICO criteria is limited. However, articles were identified which outlined what criteria reimbursement decisions are based on, which, by implication, should be incorporated into the outcomes of the assessment (and the PICO). The main drivers of decision making are the efficacy of the vaccine, the burden of disease, and the budget impact. However, other outcomes considered are the unmet clinical need, the effectiveness of the vaccine, the safety and tolerability, cost-effectiveness, public health impact, societal impact (productivity losses, travel costs, indirect medical costs, informal care), public perception of the disease and/or vaccine, and transmission models [195]. The fairness of the distribution of the risks and benefits of the vaccine across population groups is also considered [406]. However, non-uniform distribution of risks and benefits does not rule out funding on the NIP (e.g., when the risks are incurred by different people than the key benefits, such whooping cough vaccination of adults who come into contact with very young infants).

In South Korea, the sub-committee assesses data on the efficacy, effectiveness, and safety of the vaccine. Data assessed also includes the disease burden in Korea, such as the clinical characteristics of the disease, incidence, mortality, and case fatality rates. Sources of information on the vaccine include clinical trials conducted both in Korea

and in other countries, WHO position papers, and recommendations published by the USA CDC and the European Centre for Disease Prevention and Control. Economic data is reviewed by the KCDC, the sub-committee, and the KECIP and includes the cost, affordability, and financial sustainability of implementing the new vaccine program, as well as the vaccine's cost-effectiveness [200].

Patient reported outcome measures

Patient Reported Outcome Measures (PROMs) are used to provide a measure of an individual's health status. Specific guidance about the use of PROMs for vaccines was identified in the context of determining health utilities for CEA in some jurisdictions.

For Australia, the recommendations for PROMs applied to vaccines are the same as for medicines and are described in Section 2 of the *PBAC Guidelines* [285]. Generic or condition-specific outcome measures can be used. Patient-reported outcome measures may also include multi-attribute utility instruments (MAUIs), in which the scoring method for the instrument is anchored on a quality-adjusted life year scale of 0 (death) to 1 (full health). Several commonly used MAUIs for which a detailed discussion of the validity or reliability is not required are the Health Utilities Index (HUI2 or HUI3), the EQ5D-3L or -5L ('EuroQol'), the SF-6D (a subset of the Short Form 36, or SF-36), the Assessment of Quality of Life (AQoL) instruments, and the Child Health Utility 9D (CHU9D) index for children and adolescents [285].

In the UK, the JCVI uses the methodology of NICE which is the same as that used for medicines to assess the cost effectiveness of vaccines. Health effects are expressed in quality-adjusted life years (QALYs). For adults, the EQ-5D-3L is the preferred measure of HRQoL with data directly reported by patients or carers, or both. When the EQ-5D-5L has been used the 5L descriptive system should be mapped onto the 3L value set. When a recent and robust source EQ-5D data is not available, HRQoL data can be estimated by mapping other HRQoL measures or health-related benefits seen in relevant clinical trials to EQ-5D. NICE does not recommend specific measures of health-related quality of life in children and young people. A generic measure that has been demonstrated to have good psychometric performance in the relevant age ranges should be used [27].

In Canada, the QALY is used as the method for valuing health outcomes in the economic reference cases. The utilities obtained from HRQoL instruments should represent the preferences of the general Canadian population. Health preferences are obtained from an indirect method of measurement that is based on a generic classification system (e.g., EuroQol 5-Dimensions questionnaire [EQ-5D], Health Utilities Index [HUI], Short Form 6-Dimensions [SF-6D], Child Health Utility 9-Dimensions [CHU9D], Assessment of Quality of Life [AQoL]). There are currently no valid instruments for directly measuring utility in neonates, newborns, infants or young children. Utilities for child health states sourced should be obtained from a paediatric-specific generic instrument, rather than using adult utilities [410].

In Germany, STIKO carries out CEA using QALYs. It does not specify what measures of HRQoL should be used for adult or children to derive the health utilities [418].

Surrogate outcomes

In some situations, it may not be possible to measure cases of clinically apparent infection as a measure of efficacy or effectiveness (e.g., when disease incidence is too low) and in these cases correlates of protection (CoPs) can be used as a surrogate outcome.

In Australia, guidelines for vaccines to go on the PBS or NIP state that unless there are internationally accepted standards of measurement, any claims based on immunogenicity surrogates/correlates rather than clinical outcomes, need to be prespecified and justified [285]. Where the assessment is based on short-term surrogates, long-term outcomes need to be discussed, such as the waning of effect (increased likelihood of infection), and long-term sequelae [285].

In the UK, the JCVI does not provide specific guidance on use of surrogate outcomes for vaccination. However, as the JCVI use NICE methodology for economic evaluation of vaccines, the guidance from NICE on the appropriate selection and use of surrogate endpoints applied to evaluation of medicines is utilised [27].

In Canada, NACI state that immune biomarkers used as surrogate outcomes in studies of vaccine efficacy or effectiveness must meet the criteria for CoP. Multiple CoPs can exist for a single vaccine. Different vaccine types and formulations indicated for the same disease may be associated with different CoPs. The dimension of prevention (e.g., preventing infection, preventing disease, reducing severity of disease) linked to a CoP must be identified [400].

In Germany, only validated surrogates (e.g. proof of correlation of the effects on the surrogate to the effect on the patient-relevant endpoint) can be considered as endpoints, and uncertainty analyses based on their use should be carried out [418].

CDC ACIP (in the USA) recommend that surrogate outcomes should only be considered when evidence about health outcomes are lacking. If surrogates are used, it should be clear what health outcome they are a surrogate for, and the surrogate itself (such as immunogenicity) should not be listed as the measure of outcome [398].

Equity

Vaccination may improve equity by reducing the disease burden among the highest risk population groups. The Canadian NACI guidelines state that researchers and decision-makers should consider whether there are any specific groups who may especially benefit from the introduction of the proposed vaccine (for example, due to a higher incidence of cervical cancer in individuals of lower socioeconomic status), or conversely, who may not benefit [400]. Equity is a key consideration in the new framework used by Canada's NACI, and the GRADE Evidence to Recommendation framework used

by ACIP in the USA [419]. The WHO economic assessment guidelines specifically mention methods that include equity e.g., through extended-CEA to assess equity and efficiency considerations in parallel, or through distributional-CEA to assess trade-offs between equity and efficiency [182, 412].

Outcomes beyond the health of the individual

For transmissible diseases, modelling which focuses on an individual patient does not capture broader benefits of interventions. All of the key jurisdictions that had specific guidance on assessing vaccines included consideration of people beyond the individuals vaccinated. In Australia, one of the factors that influences whether a vaccine is listed on the NIP rather than the PBS, is whether there are additional health benefits to the community beyond the individuals vaccinated, such as herd immunity [420]. *PBAC Guidelines* suggest that dynamic models allow herd immunity and age shifts to be assessed. Australian guidance for vaccine assessments suggests that vaccine uptake should be commented on (and is key for its influence on herd immunity) [189].

Likewise, the UK's JCVI and the US Preventative Services Task Force incorporate broader community-wide impacts. Germany's STIKO considers the potential effects of the vaccine on individuals (effectiveness and safety), as well as total effects at the population level (considering what proportion of the population need to be vaccinated for herd immunity to protect those who are unvaccinated) [397]. In the Netherlands, the public health impact is considered, and transmission models are used [195]. The Canadian National Advisory Committee on Immunization (NACI) also provide guidance that vaccinations affect both vaccinated and unvaccinated individuals, and that there are vaccine-specific indirect effects such as herd immunity, age-shifting of disease, serotype replacement and disease eradication [400].

Non-health outcomes

A criterion used for inclusion on the NIP within the Netherlands is the acceptability of the vaccination – to the target population. This can include the associated discomfort of the vaccination, the number of doses required, and the willingness to participate in the NIP. It is stated that public support is required for any public programs, and where data are not available on the public support for a new vaccination, then the implementation strategy should include collection of these data [406]. The Netherlands also include societal impacts such as productivity losses, travel costs, indirect medical costs and informal care in their analyses [195]. ACIP in the USA use the GRADE Evidence to Recommendation framework, which incorporates consideration of the acceptability of the vaccine to key stakeholders. They survey healthcare providers in order to seek input on this [419].

In the UK, the current NICE guidelines adopted by the JCVI for economic analysis do not recommend quantitative appraisal of non-health costs [27]. Above the ICER threshold,

NICE might also consider aspects that relate to uncaptured benefits and non-health factors when developing guidance, in line with its guiding principles [27, 80].

In Canada, NACI recommends that two reference case economic evaluations are developed: one from a publicly funded health system perspective and the other from a societal perspective where non-health sector outcomes are included. Where a decision-maker is interested in comparing a vaccination program with a non-health intervention, a cost benefit analysis can be presented alongside the societal perspective reference case analysis [400]. NACI include non-health impacts such as productivity, consumption and education, as well as environmental impacts [408].

The EUnetHTA core model includes the assessment of ethical, sociocultural elements, and legal elements, which are then referred to in national guidance, such as produced by HAS in France.

RECENT CHANGES TO PRE-ASSESSMENT PROCESSES IN AUSTRALIA AND INTERNATIONALLY

- Are there recent changes to pre-assessment processes that impact on PICO development?
- Are the recent changes aimed at faster access?

Changes to pre-assessment processes

In Australia, ATAGI introduced pre-assessment processes for vaccines which came into effect 1st July 2020 [395]. These changes involved introducing templates for both the sponsor submission to ATAGI, and for ATAGI's advice to the sponsor and PBAC. The reforms also coordinated the ATAGI process with PBAC timelines and introduced the contracting of evaluation groups to provide the draft advice, which would be considered and then presented to ATAGI by ATAGI members.

Collaboration

Although an agreement has been made between Australia, the UK, Canada and New Zealand to explore implementing joint clinical assessments [381], of the member agencies, only PBAC and Pharmac are currently involved in vaccine assessments. The scope for collaboration, specific to vaccines, is therefore more limited than for medicines.

Faster access to areas of unmet clinical need

The COVID-19 pandemic demonstrated how access to vaccines in an area of high unmet can be expedited. Within a year of the pandemic being declared, COVID-19 vaccines had been developed, and received emergency regulatory approvals [421] and been recommended for use by NITAGs. In Australia, ATAGI met frequently to monitor and

advise on COVID-19 vaccine effectiveness and safety in addition to advice provided by the TGA [422]. The cost-effectiveness assessment processes of HTA that would usually be applied to vaccination programs were not utilised for making economic decisions regarding use of COVID-19 vaccines [423] due to the bespoke approach required for the procurement of vaccine supplies at a time of high demand globally. The expedited process for COVID-19 vaccine assessment reduced the timeframe (compared to the standard ATAGI and PBAC process) to roll-out of the vaccine, in the context of a national emergency and public need, and was instrumental in reducing hospitalisations and deaths.

The processes used by NITAGs in other jurisdictions for vaccine evaluation during emergency situations (such as a pandemic) are not currently well documented in the literature or on the websites of the NITAGs in key jurisdictions.

Many jurisdictions perform surveillance of communicable diseases to determine areas of unmet clinical need and perform horizon scanning to determine if there are new or emerging vaccines to be considered for inclusion on their NIP. This should assist in timely access to vaccines which address an area of unmet clinical need.

One instance of a variation in the pre-assessment process for areas of unmet need was observed in France - HAS provides early HTA advice when vaccines are developed that have a new mode of action and meet an unmet or poorly met clinical need [195].

Consideration of programmatic factors of vaccines

The guidelines for vaccine evaluation in Canada (by NACI) have recently been updated, and include an expansion from reviewing safety, efficacy, immunogenicity, effectiveness and burden of illness, to also including programmatic factors – economic, ethics, equity, feasibility and vaccine acceptability (EEFA) [96]. The programmatic factors, such as vaccine acceptability, are increasingly acknowledged by NITAGs and decision-makers around the world as being important, given the rise in vaccine hesitancy [96]. These elements are also considered by NITAGs who use the GRADE process, which incorporates the elements of feasibility, acceptability, cost and equity into the Evidence to Decision (EtD) framework (such as ICER in the USA), although it is not explicit how the evidence for these factors is incorporated into the systematic reviews that are being considered and which use GRADE [96]. The additional elements of ethics, equity, feasibility and vaccine acceptability were considered to take a few additional days to address, but separate evidence reviews were rarely needed [96].

Consideration of broader value of vaccines

The NACI guidelines for economic evaluations of vaccines, suggest that broader, non-health-related outcomes are associated with many vaccination programs, and could be relevant to assess. For example, vaccination against influenza could result in productivity-related benefits, and a vaccine for measles may prevent neurologic

damage, which has an impact on educational outcomes. In these cases, the guidelines recommend that a cost-benefit analysis is presented, as well as the reference case cost utility analysis [400]. In Australia, the guidelines for preparing submissions to ATAGI suggest that the details of nonhealth-related impacts of the proposed vaccine should be presented in 'Other relevant information' [189].

IMPLICATIONS

For most submissions made to the (ATAGI and) PBAC, the current process of determining the PICO criteria is fit-for-purpose. Anecdotal evidence from PBAC evaluation groups suggest that there is a low rate of resubmissions associated with one or more elements of the PICO being incomplete or wrong. However, there are changes that could be considered.

Areas of difference between Australia and other countries in the pre-assessment processes and determination of the PICO were used as a prompt for discussion on ways in which the Australian HTA system might be improved. Comments on the benefits and risks of these approaches below, and possible options for piloting, are based on HTA expert opinion within the context of the evidence-base that has been summarised.

ADDING A SCOPING PHASE FOR PBAC SUBMISSIONS

Australia could consider adding a scoping phase and PICO ratification process for submissions concerning medicines and highly specialised therapies appraised by PBAC. This could be achieved through pre-existing structures, such as PASC (but perhaps with additional committee member expertise in pharmaceuticals), or through a newly created PBAC subcommittee, or through a public consultation process undertaken and managed by the Department, with support from commissioned HTA agencies or evaluation groups. There is no need to do this for vaccines as ATAGI already provide pre-assessment advice on the PICO. To ensure, however, that the additional scoping phase does not unnecessarily congest the HTA evaluation and appraisal process, there are different options proposed:

- the PICO development scoping phase could be reserved for medicines that are 'first in class' as that is when there is the greatest uncertainty about the clinical place for a medicine or technology, and thus directly affects the PICO.
- Another alternative is that the applications for first in class medicines are triaged to determine how disruptive they are likely to be to the healthcare system, and those determined likely to be disruptive are required to have PICO criteria considered by stakeholders prior to the submission of the application for funding. A definition of 'potentially disruptive' would need to be pre-specified and criteria developed. A further criterion could be that the scoping phase is

reserved for medicines or highly specialised technologies where early clinical data indicates a significant clinical benefit.

- Another option is that the approach proposed for the cost recovery pathway for MSAC is also used for the PBAC, i.e., that sponsors may choose whether their medicine or technology goes through a scoping phase or bypasses it.

A separate scoping process is unlikely to be needed for medicines which are next in class (i.e. medicines with a similar mechanism of action to existing medicines for a particular condition), or those deemed non-disruptive technologies. For these, the place of the medicine and technology in clinical practice and pathway of care will have been established. For those technologies deemed disruptive, public consultation on the PICO could include consideration of the organisational impact of the proposed medicine (e.g., the States and Territories could make requests to include certain cost items in the submission).

Having a separate scoping process to develop the PICO criteria (as per the PASC of MSAC, ATAGI, EUnetHTA, NICE and ICER) allows the possibility of additional stakeholders to provide input, including patients. Benefits of this approach include being more transparent, helping ensure that the comparators are suitable for the jurisdiction, and that the outcomes discussed are relevant to patients and decision makers (or assist the PBAC in understanding how relevant the trial outcomes are to patients). For example, patient involvement in scoping of a treatment for multiple sclerosis by NICE, resulted in subgroups being identified, for whom additional comparators were relevant [287]. There might also be gains in timeliness as the approach could feasibly reduce the number of resubmissions arising from the initial submission not fully capturing the appropriate population subgroups and comparators. It is, however, acknowledged that this 'added value' might only affect a small number of submissions

Although stakeholders may comment on the outcomes deemed most relevant to patients, the clinical outcome data evaluated are dependent on the outcome data collected in the primary research. Incorporating patient input to improve the relevance of outcome measures to patients would be more influential prior to these clinical trials being performed. Granting bodies such as the National Health and Medical Research Council (NHMRC) and the Medical Research Future Fund (MRFF) are now requiring a much greater involvement of patients and consumers in grant applications for clinical trials, and so more patient-relevant outcome definition may be an end-product. However, this relates to publicly funded trials that are often, although not exclusively, coming out of Universities and medical institutes. Patient and consumer involvement in trial design is less visible for "in-house" clinical trials developed and funded by pharmaceutical companies, which are usually global.

Adding an additional scoping process to the current PBAC process would increase the time to submission and (possibly) to reimbursement, unless reimbursement occurred prior to evaluation, as per Germany, or the pre-assessment phase occurred prior to the

current PBAC/TGA parallel submission process. For MSAC applications the scoping phase is 4 months [288]. In England, although it is not explicit how long is required for the NICE scoping phase, the consultation period on the PICO varies in length depending on the level of uncertainty of the topic. If the topic has been well defined by another NICE output within the last 12 months, then the consultation period is 14 calendar days, whereas if there is a reasonable degree of uncertainty about elements of the draft scope (or if highly specialised technologies are being evaluated), there is 28 days of consultation [27]. If sponsors engaged with a pre-assessment phase at an earlier time point than when they would have otherwise submitted to the PBAC and TGA (i.e., before a full dossier is compiled), then the impact on timeliness of adding the scoping phase to the process may be mitigated. However, if started too early, there is the risk that the submission may be withdrawn (if the results of the key trial are not as favourable as expected), or that the population proposed to be eligible for the medicine changes, reducing the usefulness of the scoping process.

One risk of adding a scoping phase for "first in class" submissions to current processes, is that the advice provided by the PICO subcommittee (PASC) may not reflect the views of PBAC, or that the advice (such as the most appropriate comparator) becomes out of date by the time the submission is evaluated and then appraised by PBAC. The composition of PASC would potentially need to be altered, or an alternative subcommittee of PBAC set up to deal specifically with PBS listed technologies. Having said that, if the scoping process was restricted to cases producing the most uncertainty and decision delay, such as first in class and disruptive medicines, then these risks may be warranted, if it can reduce the number of submissions required for a positive recommendation.

Australia already has a process in place for reviewing classes of medicines once they have been established in clinical practice (PBS Post-market reviews) and that process is able to consider sequencing of treatments and thus whether the initial PICO should change after the medicine has been used widely and how the availability of new treatments available on the market might affect the population and comparator. Although this occurs after the initial submissions and funding of medicines, the process may influence new submissions to PBAC for alternative technologies or for the same medicine but for an extended population (flow on changes).

INVOLVEMENT OF STAKEHOLDERS

Consideration could be given to how input from stakeholders, such as the "patient voice" can best be encouraged and supported. As noted in the findings of this paper, codependent tests and other technologies assessed by the MSAC currently have a separate scoping phase to determine the PICO, and public consultation is sought based on information provided by the sponsors in their application form, as well as some plain language summaries of the PICO on the MSAC website. The public consultation form is the same for clinicians, patients and family members, without additional prompts on

what type of information those with lived experience are best able to provide. The public consultation form could be amended to provide guidance on areas that patient input would be most valuable. Providing patient input can place a burden on patients and patient groups, who are often volunteers, and experiencing ill health [287] and so clear guidance on what information is most valuable is warranted.

Although CADTH does not incorporate patient input into the PICO criteria for medicine submissions, they have published guidance on providing patient input, which would be relevant at the scoping stage. This guidance outlines how the patient perspective can help better understand the nature of the disease, the relevant health outcomes (what is important to patients), the diversity of needs among patients and health care settings and highlight if there are subgroups that need to be considered and identify potential issues around the patients' ability to use and access the medicine under review. If input is provided for a treatment which is subsequently reviewed for a new indication or an expanded patient population, the stakeholder input provided previously could be used again [323].

A risk of introducing an expanded public consultation process, is that sponsors may (intentionally or unintentionally) use this process as a means of trying to influence decision making. Patient groups often rely on financial support from industry such as medicine sponsors. This could feasibly place patient groups in a conflict-of-interest situation, where the group members may consciously or unconsciously feel obliged to align with the sponsor's interests and provide input that would support those interests. The same could be said for government funding of patient groups and aligning feedback with payer (and taxpayer) interests. The proportion of funding that patient groups receive from interested stakeholders may not always be transparent. This could be made more transparent by documenting it as part of the feedback process and ensuring that any individuals or organisations who provide input appropriately declare their conflicts-of-interest as per the Declaration of Interest included in PBAC's current public consultation survey form. There are also workload implications. If a patient group encourages all its members to provide input, the volume of input would result in an increase in work required by the Department (Office of HTA) and/or the PICO subcommittee to synthesise and digest the input, as well as the workload associated with incorporating the patient input. An efficient stakeholder engagement process would be proportionate, with the extent of engagement on PICO calibrated to the level of unmet clinical need and uncertainty associated with the technology.

CONDITIONAL FUNDING FOR ORPHAN MEDICINES AFTER REGULATORY APPROVAL

One option to facilitate faster access to medicines for patients with an unmet clinical need, is to use an approach similar to Germany, the Netherlands and France. In these jurisdictions, medicines for severe diseases with unmet clinical need can be reimbursed after regulatory approval, on the condition that further evidence is collected, to allow

evaluation. The development of PICO criteria in this scenario could be used be to inform the relevant data to be prospectively collected in the clinical studies (as well as define what already existing evidence should be collated).

Funding of innovative medicines prior to there being definitive evidence of the comparative safety and effectiveness can result in some patients receiving treatments which may: i) result in additional unnecessary toxicity/adverse events than if they received standard of care, ii) prevent patients receiving more effective standard of care (some patients will forgo treatments of proven clinical benefit), and iii) be effective for the individual, but not cost-effective at the population level. For coverage with evidence development (CED) schemes for orphan medicines and rare diseases, processes should be put in place to make it clear to patients/carers that the clinical effectiveness and cost-effectiveness of the conditionally approved medicine have not been established, so that they can make an informed decision about using them. Governments and HTA groups may be well placed to provide information resources on these matters, although traditionally issues of informed consent and clinical advice are – and should remain - within the remit of the treating clinician. There are also ethical questions about removing access to medicines that have been provisionally funded and are clinically effective (to some extent) for the individual but turn out to be cost-*in*effective at a population level. In these circumstances it is not an appropriate use of taxpayer funds to continue funding the medicine, given the opportunity costs. That is, the funds could perhaps have greater value in maximising population health outcomes if they were spent elsewhere. In these circumstances the role of the medicine sponsor in funding these "responder" patients would need to be considered as, if the full evidence had been presented prior to reimbursement, patients would not have received funded access to the medicine at all. There is a risk with CED schemes that the evidence generated will not reduce the uncertainty, and that further evaluation will not be able to establish the benefit/harm profile and cost-effectiveness of the medicine. Without clear expectations defined upfront about the PICO, removal of funding due to the *absence* of evidence – as opposed to clear evidence of cost or clinical ineffectiveness – would be challenging and may result in a public backlash.

A full discussion of the benefits/ risks/ limitations of funding prior to an assessment of the comparative safety/effectiveness/cost-effectiveness of the proposed intervention versus the nominated comparator is beyond the scope of the current paper. This issue is more relevant to the process of HTA, rather than to the PICO criteria, and so further discussion is provided in Paper 1.

ASSESSMENT OF ADVANCED THERAPEUTIC MEDICINAL PRODUCTS

In Australia, either MSAC or PBAC may evaluate highly specialised technologies. For example, MSAC have evaluated cell therapies (such as CAR-T). However, both PBAC and MSAC have evaluated different gene therapies. For example, onasemnogene abeparvovec for spinal muscular atrophy was evaluated by PBAC and voretigene

neparvovec for biallelic RPE-65-mediated inherited retinal dystrophies was evaluated by MSAC. Both gene therapies are delivered by adeno-associated viral vectors and are considered as one-off treatments. The Public Summary Document (PSD) for voretigene neparvovec states that the therapy was considered suitable for assessment by MSAC for joint funding by the Commonwealth and the States/Territories under the National Health Reform Arrangements (NHRA) on the basis that it will be administered to admitted patients in public hospital-based specialist treatment centres. The reason for assessment of onasemnogene abeparvovec by PBAC was not stated in the PSD of the PBAC meeting but probably related to it being dispensed as an outpatient medication. One option could be for a single pathway to be chosen (such as MSAC), which includes the scoping phase as suggested above. This would have the benefit of more consistent processes for biologics and would avoid the problem of knowing which pathway highly specialised technologies should take when they are initially administered in-hospital, and then used on an ongoing basis as an out-patient. There is the risk, however, that in the transition period resubmissions developed to address the issues raised by one committee (such as MSAC) may not address all the issues that the other committee (PBAC) may have.

POPULATION

Most jurisdictions were similar in allowing the sponsors to define the population to be assessed, if it was no broader than the patient indication agreed through regulatory approval. This is not to imply that the scoping phase does not influence the Population, as stakeholder feedback may influence important subgroups to be considered; such as those at risk of particular outcomes, or who may usually receive a different treatment than the comparator specified. Except for vaccines, most jurisdictions only focus on health outcomes for the treated individual. This has the benefit of there being well established methods for assessment of benefit, greater consistency between assessments etc. NICE state that if carer quality of life is relevant, then this should be included, without specifying whether this should be in sensitivity analyses (similar to Australia) or included in any base-case for economic modelling. An option that could be beneficial for Australia is to be explicit that assessment of antimicrobial agents or treatments and vaccines for communicable diseases, should include populations broader than the treated individuals (i.e. include those who may or may not become infected in different scenarios), and those who may or may not develop resistance to the antimicrobials.

Those jurisdictions which had separate guidance on vaccines were consistent in considering the public health implications of the vaccines, i.e., the benefits/harms of the vaccines on those who do and do not have the vaccine, such as through herd immunity.

Currently, the assessment of how new medicines affect health equity is open for sponsors to include if relevant for PBAC submissions but is not a requirement. Australia

could require more explicit consideration of impacts (and risk/benefit trade-offs) on population subgroups based on measures of equity (such as socioeconomic status or level of remoteness). The clinical trial evidence will rarely explore effects in these 'equity' subgroups because effect modification associated with the medicine, i.e., the *relative* effects varying across subgroups, is not expected. However, there is an argument that the *absolute* effects of a medicine might be larger in specific subgroups due to the capacity to access and respond to treatment and so funding medicines in these groups might contribute to greater health equity at the population level.

COMPARATORS

As Australia explores the possibility of HTA collaboration with the UK, NZ and Canada, consideration will be required around the process of determining the comparators relevant to each jurisdiction, as usual care and the established treatments registered in each country may differ.

In Australia, the *PBAC Guidelines* require that the comparator is the current practice most likely to be replaced, whereas in some jurisdictions, the comparator is recommended to be best practice (treatment recommended by national or international guidelines; regardless of access being provided to that treatment). Although using best practice may be considered conservative for the purposes of estimating incremental effectiveness of the proposed medicine, it may also underestimate the financial impact of introducing the proposed medicine. However, this would not impact on financial analyses in Australia, as Australia has formal processes for estimating financial impact based on current practice, that is not the case in some other countries.

Consideration could be given as to whether the PICO criteria should define not only the comparator for the relative safety, effectiveness and cost-effectiveness assessments, but also the range of treatments used in current practice for the financial analysis and the treatment alternatives for reference pricing purposes. For joint assessments, adding details of what treatments will likely be used for reference pricing may be inappropriate as pricing would likely occur as a separate step, given it needs to be jurisdiction-specific. The price of treatment alternatives is also unlikely to be able to be specified for stakeholder input, due to the commercially sensitive and confidential pricing arrangements between medicine sponsors and payers.

For vaccine evaluation, limited guidance was provided by most jurisdictions on determining the appropriate comparator. Canadian guidelines are explicit that both preventive approaches should be considered (e.g. alternative vaccines, screening, non-medical approaches), as well as treatment-based approaches [408]. The current Australian guidance could be expanded to be more explicit about the range of comparators that could be considered (such as through the use of illustrative examples, similar to the Canadian guidelines).

One proposal by WHO, is to incorporate the use of a reference comparator of "doing nothing", which could be used in addition to the main comparator, to show not only the incremental benefit/harm and cost of the intervention, but also the absolute benefit/harm and cost. This would add an additional burden on sponsors, evaluators and committees, with the requirement to consider multiple different analyses for each submission, and also increase the time taken to undertake the evaluation.

DEFINITION OF OUTCOMES

Similar to the proposal that the scoping phase could outline the comparators not only for the clinical assessment, it could also define the outcomes of most relevance for the economic models.

There are differences in how the jurisdictions approach incorporating outcomes for people other than the treated patient. It is assumed that any collaboration between Australia, New Zealand, the UK and Canada would be similar to the European JCAs, and focus only on clinical evidence, given the different healthcare systems and costs for treatments across the jurisdictions. There is therefore scope to retain differences in whether carer quality of life is incorporated into the base case, or in sensitivity analyses. However, in order for these to be incorporated in some jurisdictions, the combined PICO (if possible) should incorporate all of these outcomes.

For the evaluation of vaccines, the guidelines for sponsors applying for ATAGI advice already outline that the submission should consider both patient and population health, and consider access, equity and non-health-related impacts, although the base case should be limited to health-related impacts. In Canada, recently updated guidelines for vaccine evaluation require explicit assessment of ethics, equity, feasibility and vaccine acceptability, and the economic evaluation should consider health outcomes (for people vaccinated, caregivers, and broader population), health system costs (publicly funded and not publicly funded such as formal caregiver services), and non-health costs (such as productivity, future individual non-medical consumption, direct out-of-pocket costs, education and cost to the environment in antibiotic use, food and non-food waster, and carbon consumption) [408]. Australia could consider expanding the guidance provided on non-health inputs to be considered for modelling of vaccine effectiveness. This could be assisted by an impact inventory table such as the Canadian NACI provide, outlining examples of health and non-health outcomes.

LIMITATIONS OF THIS REVIEW

Only guidance documents available in English or easily translated using google translate were included in this review. Guidance documents were often not comprehensive, and further instructions were sometimes identified within submission templates. Although this review was able to summarise the guidance that was available, making the distinction between guidance that was not available and not identified/unclear was

difficult. Although published literature was identified to cross-classify and supplement guidance documents, it was difficult to know whether the methods discussed were up-to-date, as many jurisdictions have changed their processes in the last 10 years. Information on reforms were often identified through further searching, and frequently took the form of media releases rather than formal guidance documents.

This review focuses on guidance documents in different jurisdictions, and it is unknown to what extent different sponsors or HTA agencies incorporate the guidance elements which may be considered optional, or on an as-needed basis.

Documentation for how vaccines are evaluated in many jurisdictions was difficult to find.

CONCLUSIONS

Overall, the current policies and processes for developing the PICO criteria that guide HTAs in Australia are generally satisfactory for most health technologies evaluated but could be improved by introducing a PICO ratification process for PBAC assessment of first in class medicines and highly specialised technologies that are potentially disruptive. During the scoping phase, stakeholders such as patients, clinicians, State and Territory governments, industry and the Department could provide valuable input for defining the population (or subgroups) of interest, outlining current practice and health service delivery, and health outcomes considered relevant to patients and to decision makers. Well-defined PICO criteria for certain select medicines and technologies may improve the quality of an initial submission, reduce the requirement for a resubmission, and thus expedite reimbursement decision making. Work-sharing and collaboration with other countries would be facilitated by the development of a specific PICO process for certain medicines and by amending some areas of the Australian HTA guidance documents.

Paper 4: Clinical Evaluation Methods in HTA

Health Technology Assessment Policy and Methods Review Papers

March 2024

Clinical Evaluation Methods in HTA

Paper 4 in Health Technology Assessment Policy and Methods Review Papers

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Acknowledgements

We would like to thank the following people who took the time to provide assistance and/or fact checked the information included in this paper –

Ms Lydia Loke, Lead Specialist, Drug and Vaccine Evaluation, Agency for Care Effectiveness (ACE), Singapore Ministry of Health, Singapore

Dr Alric Ruether, Head of International Affairs, and Irene Urbina of the Institute for Quality and Efficiency in Health Care (IQWiG), Germany

The Department of Health and Aged Care project staff who coordinated the HTA Review and worked with AHTA on delivering each of the papers.

The HTA Policy and Methods Review Reference Committee for feedback and guidance throughout the project.

SCOPE OF RESEARCH

The research topics for Paper 4 are outlined in Research Topic section and summarised below.

The objective of Paper 4 was to compare the *clinical* HTA methods used in Australia with those used internationally, and to describe existing and new methods used in HTA as identified in the literature. The characteristics of interest in these methods included any methods used in the evaluation of clinical effectiveness and safety, with particular focus on methods applied to technologies: for rare diseases; for populations with high unmet clinical need; and, for which long-term evidence is uncertain, or the evidence is rapidly evolving. As was the case with other Papers in this series, Paper 4 sought to identify methods that were used to address equity concerns and considerations for vulnerable populations.

SUMMARY OF FINDINGS

HTA METHODS IDENTIFIED IN THE REVIEW

Methods were identified that were applied for different purposes: (1) evaluating non-randomised evidence, (2) surrogate outcomes, (3) value frameworks, (4) incorporating equity into HTA, (5), incorporating stakeholder evidence, (6), evaluating specific technologies or technologies for specific populations, and (7) methods arising from recent HTA reforms in different jurisdictions.

There were several recurring themes that emerged across publications for different methodologies that have been synthesised into overarching principles for implementing new HTA methods in Australia. The goal of these principles is to provide conditions for the use of new and existing methods in HTA to ensure the methods are used appropriately, reported adequately, and evaluated consistently. The principles identify that, in many cases, the use of more complex methodologies may present an opportunity to create comparative evidence for HTA but may be accompanied by a loss of transparency or difficulties in validation. Options presented in this report are aimed at ensuring benefits from the use of methods, such as earlier access to technologies, can be realised by minimising the risks associated with their use.

PRINCIPLES OF ADOPTING METHODS IN AUSTRALIAN HTA

- Maintain a preference for high quality evidence. Use of lower quality evidence should be justified.
- Nominated methods should only be as complex as they need to be and should balance improvements in treatment effect elicitation with any loss of transparency, interpretability and ability to validate. The use of more complex methods should be justified.
- Develop guidance for methods used in Australian HTA outlining the suitability of methods for particular use cases, how to report the method (including supporting data), and how to evaluate the method. Guidance should be regularly reviewed and updated, and therefore may benefit from being published outside of the PBAC or MSAC Guidelines.
- Establish provisional funding pathways to permit earlier access to technologies that include the reassessment of a technology recommended on the basis of methods that result in uncertain estimates of incremental benefit.
- Discourage the use of complex methods that result in considerable uncertainty where timely access to technologies is not supported by clinical need.

METHODS FOR NONRANDOMISED EVIDENCE

The review identified multiple articles and HTA agency reports describing methods for evaluating nonrandomised evidence. Nonrandomised evidence may include indirect comparisons, nonrandomised studies, novel approaches for generating control arms, predictions of treatment effect in the absence of treatment switching and real-world evidence (RWE).

Indirect comparisons

Indirect comparisons are associated with a risk of confounding, and the magnitude of benefit is less certain than established in randomised trials. However, the use of indirect comparisons is necessary in circumstances where studies do not contain the most appropriate comparator, or technologies are provided with regulatory approval on the basis of single arm studies. Despite more complex methods for comparing treatments not included in the same randomised study, such as network meta-analysis (NMA), most jurisdictions have stated a preference for simple approaches (such as pairwise indirect treatment comparisons (ITC) or the Bücher method), where appropriate. More complex indirect comparison approaches may overcome limitations of the Bücher method, however they require more resources to generate, can be challenging to develop and evaluate, may be less transparent, and in most cases where only a single comparator is of interest, the results are unlikely to be markedly different from simple approaches.

Some indirect comparison methods can reduce concerns relating to confounding associated with imbalances in prognostic differences in populations across studies. Such approaches are typically less transparent during evaluation, unless supported with the provision of individual patient data (IPD).

Given the necessity to perform indirect comparisons, HTA bodies should adopt approaches that minimise the risk associated with confounding inherent with these methods, but also balance the trade-off between more advanced methods that address confounding but may reduce transparency. Such approaches to minimising risk include requiring justifications for the use of indirect comparisons and the nominated method, preferring simple and more transparent approaches when appropriate, requiring transparent reporting that permits validation, or permitting the use of methods that result in considerably uncertain estimates only in the context of a provisional funding pathway and identified unmet clinical need.

Non-traditional evidence

Most HTA agencies indicated that, in the absence of randomised controlled trials (RCTs), nonrandomised studies (nonrandomised trials or observational studies) could be used in HTA evaluations if accompanied by an assessment of risk of bias. In some cases, the use of nonrandomised evidence was stated to be for the purpose of augmenting RCT evidence, and may involve consumer evidence, clinical practice guidelines for establishing treatment pathways, or evidence for the assessment of long-term safety. However, precise methods for incorporating nonrandomised evidence for the purpose of establishing treatment effects were uncommonly discussed in HTA agency documentation.

The literature review identified multiple studies proposing uses of non-traditional evidence in HTA, such as the generation of control arms, or the use of real-world data (RWD) to create evidence of effectiveness.

The use of nonrandomised or RWE presents an opportunity to estimate treatment effectiveness in circumstances where randomisation is unlikely to be feasible. However, authors identified multiple barriers to the interpretation of evidence based on nonrandomised studies or RWD, including risk of bias and unmeasured confounding, concerns with the quality of the data collection, lack of guidance on the appropriateness of particular data sources for addressing particular questions, and a potential loss of transparency if data cannot be provided for evaluation.

The use of nonrandomised studies and RWE should be reserved as supplementary evidence to trial data or for circumstances where randomised studies or indirect comparisons of randomised studies cannot be performed. The latter is likely to occur during the assessment of rare diseases, or as a source of data to help support a claimed treatment effect after a provisional reimbursement decision (i.e. coverage with evidence development). Where nonrandomised data are required, their use should be prespecified and supported by a protocol outlining proposed methods, multiple methods and data sources should be used to show consistency, reporting should be transparent (including the provision of IPD if required to validate the approach), and decision-risk may be mitigated if a provisional funding arrangement is applied. Guidance for the use of RWE in submissions to HTA bodies is not currently sufficient and may need to be developed further to support sponsors wishing to provide evidence generated from RWD.

SURROGATE ENDPOINTS

The use of surrogate endpoints may be relevant for diseases with very long survival, or for rare diseases or disruptive technologies where only short-term data are available. Methods for validating surrogate endpoints are well described in the literature, and currently exist for submissions to the Pharmaceutical Benefits Advisory Committee (PBAC).

The data required for the validation of a surrogate endpoint can be considerable. If the goal of HTA is to value a technology in terms of final patient-relevant outcomes, the data requirements for establishing a surrogate may present a barrier to the use of surrogates in precisely the circumstances where they may be most useful. For example, response rates for a technology for a poorly studied disease (e.g. a rare disease) are unlikely to be robustly translated to a final outcome as the data linking a change in the surrogate to an impact on the final outcome may not be available. Similarly, a new technology with a different mechanism of action (e.g. advanced therapeutic medicinal products (ATMPs)) may have an effect on the surrogate to final outcome relationship that is different to the relationship studied and identified with previous treatments. The relationship between progression-free survival (PFS) and overall survival (OS) for immuno-oncology therapies may be considerably different to the relationship studied using traditional cytotoxic chemotherapies. Therefore, in many cases where surrogate endpoints would be most useful for decision-making, their translation is also likely to be accompanied by the greatest uncertainty.

Where the use of surrogate endpoints may result in more rapid access to a technology for a disease with unmet clinical need, sponsors should adopt robust methods for the translation of surrogates, and clearly identify assumptions or limitations to the approach. HTA bodies may facilitate the use of surrogate endpoints by curating a list of previously accepted surrogate endpoints by indication and technology, and by adopting alternative listing pathways (such as provisional listings) for technologies that address high unmet clinical need and are unlikely to report on final outcomes in a timely manner.

VALUE FRAMEWORKS

A very common claim across the included studies was that HTA bodies may need to consider broader value elements than effectiveness, safety, cost-effectiveness and financial impact. Consumers and the public consistently report additional value for technologies that treat severe diseases (those with large impacts on life expectancy or quality of life (QoL)), and diseases for which there are no acceptable alternatives (commonly referred to as unmet clinical need). In addition, most value frameworks (or multiple criteria decision analysis (MCDA) models) include broader impacts on patient and caregiver wellbeing, and some include aspects of equity.

While the consideration of a broader value framework by a decision-making committee may better reflect patients' and society's preferences for healthcare spending, it may be inadequate to only state the components of the value framework. Researchers have proposed methods for explicitly considering different elements of value in pre-designed models that weight (according to societal / expert preferences) and aggregate the value of a technology into a single score. The benefits of such models, called (quantitative) MCDA, in terms of the quality of decision making or improvements in transparency, remain largely untested, and no jurisdiction has adopted MCDA approaches routinely in HTA. MCDA models may require considerable resources to generate and to evaluate (and may lengthen the time to access), may result in a loss of information, may be difficult for committees to use, and importantly may be difficult for the public to adequately understand. If there is a lack of understanding in the methods used to create the MCDA model, and to generate the inputs to the MCDA model, then arguably the use of such models may reduce transparency in decision-making.

However, there may be considerable benefits of applying a qualitative value framework approach during committee deliberations. This approach has recently been adopted by the US Institute for Clinical and Economic Review (US ICER) following a review of their committee decision making processes. The US ICER's value framework reflects the main value elements identified in the literature as being the most important (for example, attracting the greatest weight in MCDA models) to consumers and the public, yet remains relatively simple. The use of the framework is explicit, with committee members scoring (on a Likert scale) each of the elements, which the committee then considers in its final assessment of the proposed cost-effective price of a technology. Transparency of the process can be increased through the reporting of how the committee incorporated the value elements into their decision making.

Almost all technologies can be evaluated using the same value framework, which promotes consistency and fairness. However, in very specific circumstances, such as for vaccines and antimicrobial agents, the impact of a reduction in transmission of disease would also need to be considered.

The adoption of a broad value framework by a committee, that is considered at each deliberation of the evidence, may have benefits of ensuring that decision-making is aligned with society's preferences for spending on healthcare. A published value framework may also provide a guide to consumers wishing to provide input on the additional value elements of a technology that are not commonly captured in clinical studies. However, the committee should maintain a focus on the opportunity cost of healthcare spending, which may be less well captured in such value frameworks.

INTEGRATING EQUITY INTO DECISION-MAKING

Although the consideration of equity is identified in the HTA documents of several jurisdictions, little guidance is provided on how equity is considered in HTA or during committee deliberations. Australia (PBAC and Medical Services Advisory Committee [MSAC]) permits a discussion of equity issues in HTA reports, and NICE prefers such evidence to follow established methods for analysing, synthesising and presenting qualitative data.

The consideration of equity should continue to be undertaken in a deliberative fashion by committees. This may be assisted by the development of a checklist or a value framework as described above, potentially based on research and informed by public engagement, to assist HTA decision-makers to integrate equity into deliberation in a systematic way.

The potential role of quantitative methods for incorporating equity into decision making, such as Distributional Cost-Effectiveness Analysis (DCEA), remains uncertain, however should be investigated.

STAKEHOLDER INVOLVEMENT IN DECISION-MAKING

There is an increasing focus in HTA on patients' own views of what matters regarding their medical condition and treatment. Patients' views can especially find expression in patient-based evidence at the evaluation stage and in information on patients' needs, preferences, perspectives, and experiences (e.g., of treatment pathways) at the appraisal stage. Several jurisdictions apply alternative methods for capturing information for use at the appraisal stage. Canada, Singapore, Wales and other jurisdictions utilise a dedicated patient engagement team to gather the views of patients, and Belgium offers qualitative methodology guidance to collect data on patient views and experiences. However, there remains some uncertainty regarding the role and impact of patient engagement in HTA. Some frameworks for assessing impact have been used. These should be adapted and used, as appropriate. Relevant impacts of increased patient engagement would include: improvements in the confidence of patients in fair decision-making, as well as increased confidence of committee members in making well informed decisions, ultimately leading to a culture that is actively inclusive

of patient perspectives and increases trust. To support patient engagement, there needs to be greater clarity on how patient inputs are used in decision-making.

Patient involvement in HTA should be adequately resourced, being mindful of appropriate skills training as well as financial support. This may improve the relevance of the evidence received from patient groups. The role and value of public (as distinct from patient) engagement in HTA should also be investigated as this may be useful in establishing directions to support equity. Public engagement in the development of value frameworks or MCDA indicated several value elements (severity of disease, availability of an alternative) as being important to society. Insights such as these may be valuable to decision-makers.

METHODS FOR SPECIFIC POPULATIONS OR TECHNOLOGIES

Most methods for the consideration of specific populations or technologies that were identified in the literature were related to rare diseases, orphan drugs or ATMPs. Methods tended to relate to evidentiary deficiencies associated with the size of the population and subsequent uncertainties in decision-making, rather than any particular characteristics of the technologies themselves. Methods commonly cited were the application of broader value frameworks or MCDA and the use of nonrandomised evidence or surrogate endpoints.

Many jurisdictions implement different evaluation pathways for rare diseases and orphan drugs. Key features of these pathways include varying cost-effectiveness thresholds (as for the Highly Specialised Technologies (HST) programme in the United Kingdom (UK)) for orphan drugs, and the use of provisional listing with the goal of ongoing evidence generation (coverage with evidence development).

The literature did identify a key issue associated with ATMPs, in that they are very costly, and may result in considerable long term benefits to patients. Limitations in the evidence base, particularly in terms of comparative evidence and long-term data, hinder the certainty of decision-making. Common solutions proposed for reducing the risk associated with large upfront costs and uncertain benefits mainly related to the payment methods, such as managed entry agreements, annuity payments, pay-for-performance, or subscription style payments.

VACCINES AND ANTIMICROBIALS

Unlike most health technologies, vaccines and antimicrobials may have population health impacts related to a reduction in transmission of disease. These impacts can be quantitatively calculated, however models estimating these can be complex and difficult to validate. Decision-makers should incorporate the additional benefits related to impacts on transmission, if only qualitatively, in their estimate of the value of vaccines and antimicrobials.

The literature also identified a key limitation of current payment methods for antimicrobials. Most health technologies are reimbursed on the basis of sales volume. However, there may be additional value of some antimicrobials if they are reserved for specific situations, or if the antimicrobial is designed to treat a very specific microbe. Two jurisdictions have trialled payment methods that partially or fully delink the payments for the supply of antimicrobials from the sales

volumes. In both cases, the payment mechanism was negotiated to include a guarantee of supply, to prevent shortages of antimicrobials.

LITERATURE SEARCH RESULTS

The process of selecting relevant documents from grey literature (reports, guidelines and webpages of HTA agencies and governments) and peer-reviewed journal articles for this scoping review is given in the PRISMA-ScR flowchart (Figure 37).

Searches identified 142 relevant peer-reviewed articles, and an additional 35 articles were derived from citation chasing. Further relevant documents were identified from grey literature (searches of HTA agency and government websites) and targeted searches.

The documentation for many non-English speaking countries was not available in English, therefore, where possible, information was extracted from peer-reviewed journal articles.

SUMMARY OF METHODS IDENTIFIED BY JURISDICTION

SUMMARY OF THE INFORMATION AVAILABLE FROM THE WEBSITES OF HTA AGENCIES

A list of HTA agencies whose websites were searched is provided in Appendix 2.

No information could be collected from 12 out of 32 international HTA agencies included in the search. The documents on the websites for Agenas (Italy), AVALIA-T (Galicia, Spain), HAD-MSP (Uruguay), IACS (Aragon, Spain), NECA (Korea), OSTEBA (Basque, Spain), and SBU (Sweden) were not in English. There were no relevant guidelines or protocols identified on the websites for AOTMiT (Poland), and SFOPH (Switzerland). Two HTA agencies did not evaluate medicines (HTW, Wales and AHRQ, USA), and one agency did not evaluate medicines for use outside the hospital system (FinCCTHA, Finland). Hence, their methods were not included. The Pharmaceuticals Pricing Board (HILA) is responsible for evaluating medicines for reimbursement in Finland, but no relevant guidelines or protocols were identified on their website for doing or evaluating a HTA assessment.

Twenty international HTA agencies provided some information on their websites about the methods used for the evaluation of the clinical components of HTA listed above.

However, it was difficult to determine if all the guidance documents found on the websites were up to date. Especially those documents that were published several years earlier. It was also unclear whether HTA agencies used additional guidance documents from different jurisdictions, in conjunction with their own, when conducting an HTA evaluation. For example, while the OSTEBA (Basque, Spain) website did include a copy of the European network for Health Technology Assessment (EUnetHTA) HTA Core

Model Version 3.0 document, it could not be determined how closely their processes followed those used by EUnetHTA. This is also true for other jurisdictions.

Additionally, guidance documents do not provide an exhaustive list of methods – it is unclear whether methods excluded from the list are regarded as unacceptable. Very few jurisdictions clearly stated which methods would not be acceptable.

It should also be noted that the information presented here may differ from that presented in other papers. For example, there are several discrepancies with the findings in Paper 1, due to the different viewpoints taken. Whereas Paper 1 considered whether there were specialised pathways used to assess different technologies, such as medicinal products for rare diseases or codependent technologies, this paper only considered if any information about the methodologies involved in producing or evaluating a HTA report on the use of these technologies was provided, irrespective of the assessment pathway.

HTA METHODS APPLIED IN DIFFERENT JURISDICTIONS

Websites from HTA and/or government agencies involved in the evaluation of medicinal products from twenty of the included jurisdictions listed documents that identified several specific methods that are applied for the following purpose:

- evaluating non-randomised or observational studies
- evaluating non-peer reviewed data
- evaluating / incorporating consumer evidence
- identifying the patient pathway (treatment algorithm)
- identifying / monitoring long term adverse events
- weighting benefits in decision making.

Table 34 Specific methods for evaluating clinical components of HTA, by jurisdiction

Country	Organisation	Non-randomised / observational	Non-peer reviewed data	Consumer evidence	Patient pathway	Long term safety	Weighting benefits
Australia	PBAC	●	◑	●	●	●	○
	MSAC	●	●	●	●	●	○
UK: England	NICE	●	●	●	●	◑	●
Scotland	HIS/SMC	◑	○	●	○	◑	○
Wales	AWTTC	○	○	●	○	○	○
Canada	CADTH	●	○	●	○	○	○
Alberta	IHE	○	○	◑	○	○	○
Quebec	INESSS	◑	◑	●	○	○	○
Ontario	OH	○	○	●	○	○	●
Europe	EUnetHTA*	●	◑	●	●	●	○
France	HAS	●	○	●	◑	○	○
Germany	IQWiG	◑	◑	●	○	○	○
Korea	NECA	No information in English identified on website					
Netherlands	ZIN	●	○	●	○	◑	○
Taiwan	CDE	No other information in English identified on website		●		No other information in English identified on website	
USA	US ICER	●	●	●	○	●	○

Country	Organisation	Non-randomised / observational	Non-peer reviewed data	Consumer evidence	Patient pathway	Long term safety	Weighting benefits
Austria	AIHTA	No information identified on website					
Belgium	KCE	●	●	●	○	◑	○
Denmark	DEFACTUM	●	●	●	○	●	○
Finland	HILA	No information identified on website					
Ireland	HIQA	●	○	●	○	◑	○
Italy	Agenas	No information in English identified on website					
Japan	C2H	◑	○	○	○	○	○
Norway	NIPH	No information identified on website					
Poland	AOTMiT	No information identified on website					
Singapore	ACE	◑	◑	●	◑	◑	○
Spain	OSTEBA, IACS, AVALIA	No information in English identified on website					
Sweden	SBU	No information in English identified on website					
Switzerland	SFOPH	No information identified on website		●	No information identified on website		
Uruguay	HAD-MSP	No information in English identified on website					

ACE = Agency for Care Effectiveness; Agenas = The Agency for Regional Healthcare; AIHTA = Austrian Institute for Health Technology Assessment; AOTMiT = Agency for Health Technology Assessment and Tariff System; AVALIA = Galician Agency for Health Technology Assessment; AWTTC = All Wales Therapeutics & Toxicology Centre; C2H = Center For Outcomes Research And Economic Evaluation For Health; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation; DEFACTUM = Social & Health Services and Labour Market; EUnetHTA = European network for Health Technology Assessment; HAD-MSP = Health Assessment Division, Ministry of Public Health; HAS = Haute Autorité de Santé; HILA = Pharmaceuticals Pricing Board; HIQA = Health Information and Quality Authority; HIS = Healthcare Improvement Scotland; IACS = Health Sciences Institute in Aragon; IHE = Institute of Health Economics; INESSS = Institut national d'excellence en santé et en services

sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee; NECA = National Evidence-based healthcare Collaborating Agency; NICE = National Institute for Health and Care Excellence; NIPH = Norwegian Institute of Public Health; OH = Ontario Health; OSTEBA = Basque Office for Health Technology Assessment; PBAC = Pharmaceutical Benefits Advisory Committee; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; SFOPH = Swiss Federal Office of Public Health; SMC = Scottish Medical council; US ICER = US Institute for Clinical and Economic Review; ZIN = Zorginstituut Nederland.

*The EUnetHTA consortium ceased operations in September 2023. The EUnetHTA 21 deliverables will be further refined by the HTA Coordination Group (HTACG) under the European Regulation on HTA (HTAR).

● Comprehensive guidance on how to use the method to evaluate the clinical evidence is provided.

◑ The method was mentioned as being useful in evaluating the clinical evidence and/or decision-making process, but no guidance on its use was provided.

○ Unknown, as the method was not mentioned in the available guidance documents.

● The methodology is not used in the jurisdiction.

Australia

In Australia, guidance for writing HTA reports for assessing the clinical and cost-effectiveness of pharmaceuticals is provided in the PBAC guidelines (2016) [187]. The MSAC guidelines (2021) provide guidance for highly specialised medicines, such as cell-based treatments [290].

The PBAC and MSAC guidelines provide guidance on the inclusion of nonrandomised studies and non-peer reviewed studies (e.g., Clinical Study Reports). Methods useful for indirect comparisons from RCTs and non-randomised studies are discussed in the PBAC Guidelines, and reference a more comprehensive report commissioned by the Australian Government[424]. Both PBAC and MSAC guidelines provide guidance on the development of patient pathways including literature sources, the use of an expert panel and the required inclusions in the pathway. An assessment of long-term safety is also recommended in the guidelines and recommends the inclusion of periodic safety update reports, any pharmacovigilance studies (completed or ongoing post market surveillance studies), any studies identified in a separate search, including nonrandomised study designs (e.g. registry data, observational studies).

Guidance for the inclusion of consumer evidence (direct patient submissions) is provided in the MSAC guidelines and described in the Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme (Version 2.5). Neither guideline addresses the use of weighting benefits as part of the decision-making process.

UK

In England, National Institute for Health and Care Excellence (NICE), an independent HTA body, is responsible for conducting the assessment of new health technologies. In Wales, the All Wales Therapeutics & Toxicology Centre (AWTTC) has published guidance for appraising health technologies. In Scotland, Healthcare Improvement Scotland (HIS) and the Scottish Medicine Consortium (SMC) have provided guidance.

NICE provides guidance for the inclusion of nonrandomised studies, non-peer reviewed studies, and the development of patient pathways in the NICE manual (2022) [27]. NICE invites written submissions from all patient and carer organisations to provide perspectives on their experiences, to be included in the evaluation. Guidance on long-term safety was not explicitly provided. The NICE manual states that evidence from non-randomised studies may provide evidence on real-world safety and adverse events and the NICE RWE framework states that RWD can provide data on long-term outcomes. NICE has also commissioned The NICE Decision Support Unit, a collaboration of three UK Universities, to produce a series of Technical Support Documents that provide detailed guidance on how to implement appropriate methodology for specific issues in HTA and economic evaluation. The documents are available on the website of Sheffield university. A list of Technical Support Documents is presented in Appendix 5.

HIS/SMC published a guide for patient group partners in 2022[425] on preparing submissions on their experiences for incorporation into HTAs. The Patient Access to Medicines Service (PAMS) team within the AWTTC search to identify relevant patients/carers/ and patient organisations and they are invited to outline their experiences. The appraisal committees are informed of the patient perspective. Patients may be present during NICE and SMC committee deliberations.

NICE provide guidance for the weighting of benefits in decision making for highly specialised medicines in specific situations using decision modifiers. Modifiers can be considered qualitatively through discussion or quantitatively through weighting of quality-adjusted life years (QALY).

Canada

Four Canadian HTA agencies that published guidance for conducting HTAs were identified: Canadian Agency for Drugs and Technologies in Health (CADTH), Institute of Health Economics (IHE) in Alberta, Institut national d'excellence en santé et services sociaux (INESSS) in Quebec, and Ontario Health (OH).

The only agency to publish guidelines for HTA of medicines was INESSS. However, the other three agencies published some documents that provided some guidance for some components of HTA.

The INESSS Drug Submission Guidelines (2022) indicate that the results of at least one controlled randomized clinical trial (published or manuscript) must be submitted [426]. In exceptional circumstances, when an RCT is impossible to conduct other study types can be submitted with justification. Real environment evidence and data can also be submitted in order to better support the evaluation of the drug. Guidance on the information to be extracted from the real environment evidence is also provided. Patient and caregiver evidence can also be provided; however this is done through patient experts rather than organisations.

CADTH published documents about the use of RWE [427] from non-randomised and observational studies and consumer evidence [275]. IHE also published a document discussing how to integrate consumer evidence into HTA [428].

OH investigated a MCDA approach to aid decision making but did not endorse this methodology [429]. The consensus decision was "that structuring decision making in this way introduces a degree of rigidity into the process that was, on balance, undesirable."

Europe

EUnetHTA provides guidance for the types of studies to be included in the assessment of clinical effectiveness of a medicinal product. The EUnetHTA guidance document "Core Model Version 3.0" from 2016[136] indicates that non-randomised intervention studies or observational studies can be considered in cases where an RCT is not feasible, or where complementary data is presented to support RCT evidence. It also suggests

that the inclusion of registry data which reflects clinical routine care is helpful in judging whether the outcomes in the RCT are comparable to clinical practice. The Core Model also noted that data for innovative technologies may need to be supplemented with grey literature (includes non-peer reviewed and non-published literature).

Assessments require an overview of treatment alternatives, including the proposed technology. Management pathways should be guided using clinical guidelines, recommendations and published utilisation reviews. It is suggested that flowcharts are illustrative in reporting management pathways.

The EUnetHTA Core Model indicates that an assessment of patient and caregiver aspects should not be a separate process within an HTA and acknowledged that patient-related outcomes can have a major impact on the content and conclusions of an HTA report. The HTA assessor should decide whether the central questions can be answered based on existing studies or whether there is a need for evidence collection from patient groups.

EUnetHTA considers the long-term safety of medicinal products and noted that this information is not found in RCTs, rather in observational studies (cohort, case-control, and cross-sectional studies), the European Union (EU) and the US Food and Drug Administration (FDA) pharmacovigilance databases and manufacturers' periodic safety update reports.

EUnetHTA did not provided guidance on the weighting of benefits.

France

The Haute Autorite de Sante (HAS) document titled, "Transparency Committee doctrine. Principles of medicinal product assessments and appraisal for reimbursement purposes (2020)" indicated that in certain situations, real world data may be accepted by the Transparency Committee if it can be justified by the company [430]. These situations may include concomitant developments, specific populations for whom extrapolation of efficacy can be performed on the basis of pharmacokinetic data or real-life data, etc. The document implied that the place for real-life (observational) studies was as part of a post-registration assessment. The Methodological Guide titled, "Real-world studies for the assessment of medicinal products and medical devices (2021)" aims to support the use of real-world studies to optimise the level of evidence of these studies and confidence in their results for health products assessed by HAS assessment committees [431]. The guide noted that the collection of observational data in real-world conditions may modify the medicinal product's beneficial effect in terms of morbidity and mortality.

HAS created an open, online process that enables patient and consumer groups to contribute to HTA to aid decision-makers with reimbursement decisions[131].

The Transparency Committee document also noted the need for a clinical care pathway but provided no guidance on the development of this pathway.

Germany

An application for a medicinal product is made to the Federal Joint committee (Gemeinsamer Bundesausschuss: G-BA). The G-BA commissions Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)to undertake an assessment report. The patient perspective is considered on the basis of a questionnaire sent to affected persons/patient organisations at the beginning of the assessment. The information provided is considered for relevant outcomes and important subgroups.

The IQWiG General Methods Version 6.1[432] guide states that the use of non-randomized studies as proof of the causality of an intervention requires particular justification or specific preconditions and special demands on quality and only uses non-randomized intervention studies or observational studies in justified exceptional cases. It considers non-randomized comparative studies to have a low qualitative certainty of results.

IQWiG attempts to minimize the consequences of publication and reporting bias by searching beyond bibliographic databases, IQWiG conducts additional searches in trial registries and sends requests to third parties concerning the transfer of data, especially to manufacturers for unpublished results.

The IQWiG General Methods guide recommends that a care pathway describing treatment processes for patients should be developed for the therapeutic area. The General Methods guide notes that the recommended study duration for establishing effectiveness and safety are specific to therapeutic indications, published by regulatory authorities. However, it does not provide specific guidance on reporting long-term safety outcomes.

The IQWiG General Methods guide describes a process of 'weighing' benefits and harms. This process considers characteristics such as age, gender and personal circumstances. However, it remains unclear whether the same quantum of benefits might be weighted according to different patient or disease characteristics.

Netherlands

The Zorginstituut Nederland (ZIN) Guideline for economic evaluations (2016) noted that the results of RCTs are not always available and that in certain situations non-randomized or non-comparative studies will suffice, such as when the natural course of a condition is known or in the case of rare diseases [433]. Additionally, observational studies may identify long-term effects or side-effects that are not picked up in RCTs.

The guideline also reported that when non-randomized studies are utilized, potential bias must be fully explored and reported using GRADE and be taken into account in the economic evaluation.

ZIN appears to have a patient consultation process for HTA[434], however precise details of how this is undertaken have not been found.

Taiwan

Although the HTA documents were not in English, a publication in Frontiers in Medical Technology by Chen, Huang and Gau (2022) reported that various mechanisms have been developed to involve patients, caregivers, and patient organisations in both the HTA and the reimbursement process in Taiwan [132].

USA

The US ICER 2020-2023 Value Assessment Framework [32] indicates that when benefits and harms occur over the course of many years, or when harms are rare but clinically important, evidence from published peer-reviewed studies using observational data and methodologies such as cohort studies, case-control studies, and long-term disease and drug registries may be useful. The US ICER methods guide [333] indicated that if data for important patient reported outcomes have not been collected a comprehensive literature review to identify published, peer-reviewed observational studies providing this information should be conducted. Real-world evidence (both published and grey literature) may help complement other types of evidence in assessments of comparative clinical effectiveness.

The methods guide also indicated that the US ICER seeks input from healthcare stakeholders including patients and advocacy organisations throughout the HTA process. Formal feedback on the US ICER's research can be provided during an Open Input Period, in response to a draft scope, in response to a Draft Evidence Report, or during the public meeting.

Belgium

The Belgian Health Care Knowledge Centre (KCE) Process Book [435] provides guidance on the inclusion of non-randomised studies and non-peer reviewed data. Although long-term safety is not specifically stated, the section on adverse effects discusses the use of evidence beyond RCTs, which would capture any known long-term health effects.

It also provides methodology for obtaining qualitative data such as patient interviews and focus groups to provide the most relevant information and cover all variability around the proposed treatment. Both of which could be used to provide consumer evidence. The weighting of benefits in decision making was not discussed.

Denmark

The Danish Health Authority HTA Handbook (2007) includes guidance on the use of non-randomised studies and non-peer reviewed data [139]. It also provides guidance on reporting of patient aspects in HTA, this may include social aspects, an individual's aspects, ethical aspects, and economic aspects. Information is provided for generating data via individual interviews and focus group discussions to provide consumer

evidence. The handbook states that an assessment of the harms must include both short and the long-term adverse effects. This includes safety data from cohort studies, pharmacovigilance or registry data.

Ireland

The Health Information and Quality Authority (HIQA) Guidelines for evaluating clinical effectiveness of health technologies in Ireland (2018) noted that RCTs are often used in interventions for non-rare diseases and are of short duration [436]. Additionally, the choice of comparator may be affected by ethical considerations. It also noted that RCT evidence may not be always available. Thus, it allows for the inclusion of non-randomised studies. The guidelines also noted that to ensure robustness and to minimise publication bias, all attempts should also be made to include unpublished and partially published studies, assessed using the same validity criteria as the published studies. The guidelines also noted that sufficient follow up is required to capture important adverse events such as mortality and that trials usually have relatively short follow-up periods. However, there is no guidance provided for the collection of long-term safety data.

The HIQA Guide to HTA at HIQA (2016) indicated that key stakeholders (including patients and/or patient groups) have direct involvement in the HTA by forming an expert advisory group, which provides clinical, patient and organisational perspectives [437]. The HIQA Guidelines for stakeholder engagement in HTA in Ireland (2014) indicate that consumer evidence can also be provided via public consultation, whereby a draft document is made available for feedback to be provided within a defined time period [140].

Japan

The Center for Outcomes Research and Economic Evaluation for Health (C2H) Guideline for preparing cost-effectiveness evaluation to the central social insurance medical council (2022) reports that non-randomised studies, such as observational studies can be included when no RCTs are available, however, sufficient explanation regarding the research quality is needed. No guidance was provided for the inclusion of non-peer reviewed data, consumer evidence, long-term safety data, the inclusion of patient treatment pathways or the weighting of benefits in decision making [438].

Singapore

The Agency for Care Effectiveness (ACE) Drug and Vaccine Evaluation Methods and Process Guide (2021) noted that non-randomised studies may provide useful supplementary evidence about long-term outcomes, rare events and populations that are typical of real-world practice and that attempts should be made to identify evidence that is not in the public domain, such as clinical study reports [439]. The guide also

requests information about the position of the drug in the treatment pathway. No guidance was provided for the weighting of benefits in decision making.

The ACE Process and methods guide for patient involvement (2023) indicates that consumer evidence is mostly included in the form of questionnaires or survey responses [440].

HTA METHODS APPLIED FOR SPECIFIC TECHNOLOGIES OR POPULATIONS IN DIFFERENT JURISDICTIONS

Websites from HTA and/or government agencies involved in the evaluation of medicinal products from twenty-one of the included jurisdictions, listed documents that identified specific methods that are applied to the clinical evaluation component of HTA for the following populations or technologies:

- Technologies for rare diseases or small populations (limited data)
- Populations with an unmet clinical need (distinct from populations with rare diseases)
- Equity considerations for vulnerable and disadvantaged populations
- Codependent technologies (use of medicines guided by companion diagnostics)
- Emerging technologies with limited data of long-term outcomes
- Technologies or indications with rapidly a changing evidence base

Unmet clinical need was usually assessed when evaluating technologies for small populations with rare diseases. Methodologies for assessing a technology indicated for a population with unmet clinical need were only considered to be a distinct methodology if the unmet need was not part of the rare disease designation.

Table 35 Methods for addressing selected clinical evaluation challenges, by jurisdiction

Country	Organisation	Rare diseases or small populations (limited data)	Unmet clinical need	Equity considerations in vulnerable and disadvantaged populations	Codependent technologies	Emerging technology (limited data on long term outcomes)	Rapidly changing evidence base
Australia	PBAC	●	●	●	●	○	○
	MSAC	○	●	●	●	○	○
UK: England	NICE	●	●	●	●	○	○
Scotland	HIS/SMC	●	○	○	○	○	○
Wales	AWTTC	◑	○	○	○	○	○
Canada	CADTH	◑	◑	○	●	○	◑
Alberta	IHE	○	○	○	○	○	◑
Quebec	INESSS	◑	◑	○	●	○	○
Ontario	OH	○	○	○	○	○	○
Europe	EUnetHTA*	◑	○	◑	◑	○	○
France	HAS	●	●	●	●	○	○
Germany	IQWiG	◑	○	◑	●	○	○
Korea	NECA	No information in English identified on website					
Netherlands	ZIN	●	○	○	○	○	○
Taiwan	CDE	●			No other information in English identified on website		

Country	Organisation	Rare diseases or small populations (limited data)	Unmet clinical need	Equity considerations in vulnerable and disadvantaged populations	Codependent technologies	Emerging technology (limited data on long term outcomes)	Rapidly changing evidence base
USA	US ICER	◑	○	○	○	○	○
Austria	AIHTA	●	○	○	●	○	○
Belgium	KCE	●	○	○	○	○	○
Denmark	DEFACTUM	○	○	●	○	○	○
Finland	HILA	No information identified on website					
Ireland	HIQA	◑	○	◑	○	○	○
Italy	Agenas	No information in English identified on website					
Japan	C2H	No information identified on website					
Norway	NIPH	●	○	○	○	○	○
Poland	AOTMiT	No information identified on website					
Singapore	ACE	●	◑	○	○	○	○
Spain	OSTEBA, IACS, AVALIA	No information in English identified on website					
Sweden	SBU	No information in English identified on website					
Switzerland	SFOPH	No information identified on website					
Uruguay	HAD-MSP	No information in English identified on website					

ACE = Agency for Care Effectiveness; Agenas = The Agency for Regional Healthcare; AIHTA = Austrian Institute for Health Technology Assessment; AOTMiT = Agency for Health Technology Assessment and Tariff System; AVALIA = Galician Agency for Health Technology Assessment; AWTTC = All Wales Therapeutics & Toxicology Centre C2H = Center For Outcomes Research And Economic Evaluation For Health; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation; DEFACTUM = Social & Health Services and Labour Market; EUnetHTA = European network for Health Technology Assessment; HAD-MSP = Health Assessment Division, Ministry of Public Health; HAS = Haute Autorité de Santé; HILA = Pharmaceuticals Pricing Board; HIQA = Health Information and Quality Authority; HIS = Healthcare Improvement Scotland; IACS = Health Sciences Institute in Aragon; IHE = Institute of Health Economics; INESSS = Institut national d'excellence en santé et en services sociaux; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee; NECA = National Evidence-based healthcare Collaborating Agency; NICE = National Institute for Health and Care Excellence; NIPH = Norwegian Institute of Public Health; OH = Ontario Health; OSTEBA = Basque Office for Health Technology Assessment; PBAC = Pharmaceutical Benefits Advisory Committee; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; SFOPH = Swiss Federal Office of Public Health; SMC = Scottish Medical council; US ICER = US Institute for Clinical and Economic Review; ZIN = Zorginstituut Nederland.

*The EUnetHTA consortium ceased operations in September 2023. The EUnetHTA 21 deliverables will be further refined by the HTA Coordination Group (HTACG) under the European Regulation on HTA (HTAR).

● Comprehensive guidance on how to use the method to evaluate the clinical evidence is provided.

◑ The method was mentioned as being useful in evaluating the clinical evidence and/or decision-making process, but no guidance on its use was provided.

○ Unknown, as the method was not mentioned in the available guidance documents.

● The methodology is not used in the jurisdiction.

Australia

The Australian HTA processes permit the presentation of additional relevant information that may influence decision making and provides guidance for this in PBAC [187] and MSAC [290] guidelines. The PBAC guidelines includes a claim for 'rule of rescue' in very small patient populations with a severe condition where no alternative treatments exist.

Australia also has a separate program (the life-saving drugs program, LSDP) for the reimbursement of costly drugs for some rare diseases [144].

Both guidelines also provide guidance on including information about equity issues and unmet clinical needs for defined populations or population subgroups. This information may influence the decision-making process. In Australia, the drug and test of a codependent technology are reviewed as one package; both the PBAC and MSAC guidelines provide guidance on assessing codependent technologies. Neither guideline discuss the assessment of emerging technologies or technologies with a rapidly changing evidence base.

UK

NICE provides guidance for qualitative discussions about equity considerations and the evaluation of companion diagnostics (codependent technologies) in the NICE health technology evaluations manual (2022) [27]." The manual states that the diagnostic accuracy of the companion diagnostic, when appropriate, should be incorporated into the economic evaluation. The manual also provides some guidance on the assessment of technologies for rare diseases where the evidence is limited.

The NICE Promising Innovative Medicines (PIM) designation is a pathway for the early access to medicines scheme (EAMS) in areas of unmet medical need [441]. NICE anticipates that before the EAMS period starts, all EAMS products will already have been selected for a NICE Technology Appraisal or HST evaluation, which follows the normal published processes and methods. No guidance specific to emerging technologies or technologies with a rapidly changing evidence base was identified.

HIS also provided guidance for evidence generation for ultra-orphan medicines, which are used to treat rare diseases [425]. The AWMSG appraisal process includes the Wales Patient Access Scheme (WPAS), which provides a pathway for making high-cost medicines affordable for NHS Wales [240].

Canada

CADTH had no separate review process for drugs for rare diseases, but special consideration for rarity of condition, (small) population, and the absence of an alternative therapy are considered when making recommendations [442]. No specific

methodologies were discussed for rare diseases. Procedures for CADTH Reimbursement Reviews (2023) notes that the clinical utility of the companion diagnostic should be included in the application and the price should also be disclosed, if applicable [443]. CADTH is proposing time-limited reimbursement recommendations to ensure timely access to promising new therapies (with conditional regulatory approval based on early-phase clinical data) for serious conditions where there is unmet medical need. Reimbursement would be contingent on a future reassessment of additional evidence that addresses the uncertainty with the comparative clinical benefit and cost-effectiveness [443]. IHE has proposed the life-cycle-HTA framework to deal with continually emerging evidence [444]. Initial decisions may be invalidated by changes in the evidence base for the technology or by changes in the clinical pathway.

The INESSS Drug Submission Guidelines (2022) provides guidance on the identification of the unmet health need in the intended patient population and the determination of the level of this need [426]. It also provides some guidance on the incorporation of study data for drugs treating rare diseases, however, this guidance is very limited. The Guidelines also provided guidance on the evaluation of a companion diagnostic test. The evaluation must be submitted to the sector of Biologie médicale et génomique of INESSS. The guidelines do not provide guidance as to how the test should be incorporated into the economic and budgetary sections of the submission.

Europe

The EUnetHTA Core Model Version 3.0 (2016) states that specific issues about orphan drugs are not currently considered in the clinical effectiveness domain [136]. However, it also refers to Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. The purpose of this Regulation is to provide incentives for the research, development and availability (marketing) of designated orphan medicinal products. No further information was provided.

The Core Model also provides guidance on incorporating equity considerations in vulnerable and disadvantaged populations into the HTA. The guidance document also notes that the assessment should specify and explain how companion diagnostics should be used to identify eligible patients in the ‘G0009 Assessment element card’ but no further guidance is provided.

France

Guidance documents providing information on assessing drugs for rare diseases and for unmet clinical need [54], as well as for codependent technologies [445] were identified. HAS also provides scope of discussing equity issues in vulnerable and disadvantaged populations within the ‘principle of Justice’ in an assessment of ethical aspects of a medicinal product [446].

Germany

The IQWiG General Methods Version 6.1 (2022) guide states that biomarkers used within the framework of personalised medicine should also be evaluated with the methods described in the guide for diagnostic tests [432]. The guide also provides scope for assessment of equity considerations in vulnerable and disadvantaged populations within an ethics analysis. The guide also indicates that if an extremely rare disease or a very specific disease constellation is being assessed, it should be specified and explicitly highlighted in the report plan.

Netherlands

The ZIN report on Conditional reimbursement of health care (2012) provided guidance on the conditional entry of a medicine for reimbursement [447]. The condition is that data must be collected on effectiveness and/or cost-effectiveness to be used to take a decision on the permanent entry of the medicine. This includes orphan drugs.

Taiwan

Although the documents on the CDE website were not in English, a publication by Hsiang et al (2021) reported that the Rare Disease and Orphan Drug Act increased the availability of orphan drugs [51]. However, this publication does not describe the methods required to submit a HTA for an orphan drug.

USA

The US ICER modifies its approach to value assessment for treatments of ultra-rare conditions [333]. The US ICER does not change its standards for rating the evidence of comparative clinical effectiveness but highlights the potential challenges of generating high quality evidence for the interventions being evaluated. The modified framework also gives greater weight to the intervention's impact on patient and caregiver productivity, education, disability, and other societal considerations.

Austria

The Decision Support Document Nr. 77 on procedural guidance for the systematic evaluation of biomarker tests (2014) was available in English and provides guidance, including the use of linked evidence, for the evaluation of co-dependent technologies [448]. A review on patient access to drugs for rare diseases in Austria commented that there are currently no specific assessment or reimbursement pathways for orphan drugs in Austria.

According to the RARE-IMPACT document (2020) on the challenges and proposals for improving patient access to ATMPs in Austria there are no specific assessment or reimbursement pathways for orphan drugs in Austria [449].

Belgium

The KCE Report 112C: Policies for Rare Diseases and Orphan Drugs (2009) reported that orphan drugs follow the same procedure as Class I pharmaceutical products, for which the company claims a therapeutic added value [88]. However, unlike for Class I pharmaceutical products, no pharmacoeconomic evaluation must be submitted for orphan drugs.

Denmark

The Danish Health Authority HTA Handbook (2007) states that "ethics do not hold a clearly defined place" in the Danish HTA model. However, the handbook supports a discussion on equity under the principle of justice within the ethical considerations section and is included under patient aspects in the model [139].

Ireland

The HIQA Guidelines for evaluating clinical effectiveness of HTA in Ireland (2018) noted that when limited data is available, such as for rare diseases, results from pre-specified interim analyses (often with an intermediate outcome instead of the pre-specified endpoint) may form the basis of a conditional marketing authorisation pending final approval based on analysis of the pre-specified endpoints [436]. This suggests that special consideration is given to orphan drugs but no further information was available.

The HIQA Guidelines for the Economic Evaluation of HTA in Ireland (2019) noted that achieving equity of healthcare is a key consideration of decision-makers [91]. Thus, an attempt should be made to include equity considerations, such as highlighting unmet needs of disadvantaged groups, in the report. No further guidance was provided. The potential impact of a technology in addressing this concern should also be discussed.

Norway

There are no specific guidelines for assessment of pharmaceuticals for rare diseases in Norway. However, a memorandum, written by a working group with representatives from the Norwegian Institute of Public Health (NIPH), describes the arrangements for single technology assessments of pharmaceuticals (2018) noted that different requirements for documentation of benefit than for other interventions may be required as the patient group can be too small for traditional RCTs to be carried out [164]. Also a higher level of resource use may be acceptable for these patients as industry may have weaker incentives to develop medications for smaller patient groups.

No guidance for populations with a high unmet clinical need, equity considerations in vulnerable and disadvantaged populations, codependent or emerging technologies, or technologies with a rapidly changing evidence base was identified.

Singapore

The ACE Drug and Vaccine Evaluation Methods and Process Guide (2021) included an addendum on the evaluation methods and processes for medicines under consideration for inclusion in the Rare Disease Fund [439]. It also noted that manufacturers who were unsuccessful in achieving a subsidy listing for their products on the basis of uncertain or unacceptable cost-effectiveness or budget impact will be allowed to resubmit a revised price proposal once for the Drug Advisory Committee (DAC) to reconsider. In some instances, where there is a high unmet clinical need, manufacturers may be contacted for price resubmissions earlier.

METHODS USED IN HTA

The planned scope of the review included multiple methods intended to address key uncertainties in HTA. Many of the methods identified are relevant to more than one research question proposed in the Terms of Reference.

Additionally, the precise definition of a 'method' is difficult to apply to all the articles identified in the scoping review. In some circumstances, articles describe concepts or approaches that could be applied in HTA, but do not necessarily discuss complete methods that would be required to enact the approaches. An example of this might be articles reporting on value frameworks. Such articles describe the advantages (and sometimes disadvantages) or adopting broader value frameworks in HTA, often in particular circumstances, however, do not necessarily describe the methods required to collect additional data or analyse evidence to populate an evaluation of a technology.

Finally, several methods may have implications for the economic evaluation of health technologies. Where methods contain a clinical evaluation component (for example, the estimate of the treatment effect or of additional benefits), they have been retained and discussed.

NONRANDOMISED EVIDENCE AND OBSERVATIONAL STUDIES

There are several methods used to analyse clinical data from non-randomised evidence. In general, non-randomised evidence informs the incremental benefit or safety of an intervention compared with a comparator in which the two treatment arms were originally non-randomised or randomisation has been compromised due to efforts to adjust for treatment switching, or consideration of non-stratified/exploratory patient subgroups. The methods used to estimate the treatment effect of an intervention vary depending on the type of available evidence. Examples of non-randomised evidence

considered in this report include the estimation of the incremental treatment effect (either benefit or safety) in the following circumstances:

- The intervention and comparator data are sourced from different studies;
- The comparator effectiveness or safety is described by a historical control;
- The intervention and comparator data are sourced from the same study where the comparator is concurrent);
    - The intervention and comparator arms were not originally randomised (for example a prospective cohort study comparing two treatment arms);
    - The intervention and comparator arms were originally randomised, however randomisation is affected by methods for adjusting for treatment switching or comparing exploratory subgroups of patients (i.e., not a stratification factor at randomisation). Meta-regression and subgroup analysis usually represent **observational evidence** as the characteristic they regress on is not randomised;
- The intervention and comparator data are sourced from the same study (and same participants) with a pre-post ('before and after') design in which effectiveness and/or safety is measured during a period prior to the intervention (intraindividual comparisons).

Indirect comparisons

HTA Agency websites from the included jurisdictions were searched to identify specific methods for evaluating indirect comparisons. Specific methods were mentioned by seven jurisdictions: Australia (PBAC), UK (NICE), Canada (CADTH), Europe (EUnetHTA), France (HAS), Ireland (HIQA) and USA (US ICER). The methods described by these jurisdictions are listed in Table 36.

Three primary methods for doing indirect comparisons using aggregate trial data were identified.

- Bücher ITC(6 jurisdictions)
- Bayesian mixed treatment comparisons (MTC) (7 jurisdictions)
- Lumley NMA for Indirect Treatment Comparisons (3 jurisdictions)

Bücher ITC was referred to as an 'adjusted indirect comparisons' in the HAS (France) documents. It is often used for a simple indirect comparisons, such as for an indirect comparison of A versus C, using studies comparing A versus B and B versus C. Three jurisdictions (Australia, France, and Ireland) described an indirect comparison based on pooled data derived from meta-analysis of grouped trials; this is also a Bücher ITC methodology. Although it was noted that obtaining sufficient studies to conduct a meta-analysis is becoming less frequent, such that most indirect comparisons are now mostly based on single studies. The Bücher ITC method can also be used in a star-shaped network of treatments, where several different interventions are compared to a common comparator.

Bayesian Mixed Treatment Comparisons (or NMA) was mentioned by all seven jurisdictions and discussed in some detail by six. Lumley NMA for Indirect Treatment Comparisons, a frequentist NMA method, was mentioned by 3 jurisdictions.

NMA models have been developed using Bayesian and frequentist frameworks. Bayesian methods utilise prior distributions to estimate the effect of the intervention, and frequentist methods are based on repeated sampling with the characteristics of the population being fixed. EUnetHTA also described NMA methods using time-to-event data, which can be derived from published Kaplan–Meier survival curves.

Three jurisdictions reported three different population-adjustment methods (Table 36) for performing an indirect comparison:

- Matching-Adjusted Indirect Comparisons (MAIC) (PBAC, NICE, EUnetHTA),
- Simulated Treatment Comparisons (STC) (PBAC, NICE, EUnetHTA),
- Multi-Level Network Meta-Regression (ML-NMR) (NICE, EUnetHTA).

These methods require IPD for at least one trial in the indirect comparison. The PBAC guidelines recommend the use of MAIC or STC to correct for trial differences and improve transitivity where IPD are available for at least one study.

Table 36 Methods for evaluating indirect comparisons

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Indirect comparisons using aggregate trial data			
Bücher Indirect Treatment Comparison (ITC)	Comparison of the effect of A versus B and of the effect of B versus C to obtain an indirect comparison of A versus C, using B as the common denominator. If multiple studies of a single comparison are available, they can be pooled using standard meta-analysis methods. The Bücher ITC method can also be used in a star-shaped network of treatments, where several different interventions are compared to a common comparator.	It is assumed that the study population, study design, outcome measurements, and the distribution of treatment effect-modifiers is the same in all trials included in the indirect comparison. It should not be used when multiple trials have been pooled using random-effects meta-analysis. This method is not appropriate when using more complex networks of treatments with multi-arm trials. Multi-arm trials can only be included as pairwise comparisons.	Australia (PBAC) PBAC Guidelines (2016) [187] Canada CADTH Indirect Evidence (2009) [450] France (HAS) Indirect comparisons (2009) [451] Europe (EUnetHTA) D4.3.1: Direct and indirect comparisons (2022) [452] Ireland (HIQA) Guidelines for Evaluating the Clinical Effectiveness (2018) [436]
Bayesian Mixed Treatment Comparisons (MTC)	A NMA method. To evaluate the relative efficacy between two treatments using a network of available evidence. This approach can incorporate both indirect and direct evidence.	It is assumed that the true effect of a given treatment is the same in all trials included in the indirect comparison. Bayesian MTC methods are particularly useful in situations with sparse data. But can be complex and do not lend themselves to easy application or interpretation. MTCs may require non-standard statistical software, and evaluators may require the programming code to replicate the results.	Australia (PBAC) PBAC Guidelines (2016) [187] Canada CADTH Indirect Evidence (2009) [450] France (HAS) Indirect comparisons (2009) [451] Europe (EUnetHTA) D4.3.1: Direct and indirect comparisons (2022) [452] Ireland (HIQA) Guidelines for Evaluating the Clinical Effectiveness (2018) [436] UK (NICE) Process and methods manual (2022) [27] USA (US ICER) Methods for HTA (2020) [333]
Lumley Network Meta-analysis for ITCs	A random-effects frequentist model for an indirect comparison between two treatments of interest Allows the combination of both direct and indirect evidence and requires a closed loop structure.	It is assumed that the relative effectiveness of a treatment is the same across all trials and varies around an overall average treatment effect. Requires a closed-loop structure.	Canada CADTH Indirect Evidence (2009) [450] France (HAS) Indirect comparisons (2009) [451]

Method	Purpose	Requirements/Assumptions/Limitations	Reference
			Ireland (HIQA) Guidelines for Evaluating the Clinical Effectiveness (2018) [436]
Network meta-analysis (NMA) using time-to-event data			
NMA with flexible survival time models	NMA without the assumption of proportional hazards requires flexible models for the hazard function. These methods require IPD or pseudo-IPD time-to-event derived from published survival curves.	A limitation is that the estimated treatment effects are not easily interpretable and testing for statistically significant treatment effects cannot be performed.	Europe (EUnetHTA) D4.3.1: Direct and indirect comparisons (2022) [452]
NMA of restricted mean survival time (RMST)	When the proportional hazards assumption does not hold. A relevant follow-up time-point is selected and the area under the Kaplan–Meier curve between randomisation and the time point are calculated. Relative treatment effects are then computed as either the difference or ratio of RMSTs between treatment arms.	Results may vary depending on the choice of follow-up time. Possible follow-up times are limited by the available data, with some longer timepoints being more uncertain due to the limited number of patients at risk.	Europe (EUnetHTA) D4.3.1: Direct and indirect comparisons (2022) [452]
Population-adjustment methods			
Matching-Adjusted Indirect Comparisons (MAIC)	MAIC is a propensity score method used for population adjustment. IPD from one trial is used to match baseline summary statistics reported from another trial, such that treatment outcomes are compared across balanced trial populations.	Requires IPD for at least one of the included studies. The principal concern is whether the weighted pseudo-population has the same distribution of baseline characteristics as the target population. To assess this the extent of overlap between the two populations should be determined.	Australia (PBAC) PBAC Guidelines (2016) [187] UK (NICE) NICE DSU: CHTE2020 (2020) [453] and NICE DSU TSD 18 (2016) [454] Europe EUnetHTA D4.3.1: Direct and indirect comparisons (2022) [452] and D4.3.2: Direct and indirect comparisons (2022) [455]
Simulated Treatment Comparison (STC)	Indirect comparisons of two treatments after regression adjustment for population differences between the two studies. It involves using IPD and linear regression modelling of the relationship between population characteristics and outcome. The model is then used to estimate that outcome for other trials.	Requires IPD for at least one of the included studies. The trials must be comparable in design, differing only in the profiles of their populations. A robust method when all effect modifiers have been identified and included in the adjustment model. However, the result may be biased if an effect modifier is missing,	Australia (PBAC) PBAC Guidelines (2016) [187] UK (NICE) NICE DSU: CHTE2020 (2020) [453] and NICE DSU TSD 18 (2016) [454] Europe EUnetHTA D4.3.1: Direct and indirect comparisons (2022) [452] and D4.3.2: Direct and indirect comparisons (2022) [455]
Multi-Level Network Meta-Regression (ML-NMR)	ML-NMR is both a regression adjustment method and an extension of the NMA framework. It incorporates any mixture of IPD and aggregate data from any connected network.	When ML-NMR is used in larger networks, checks for heterogeneity and inconsistency should be undertaken.	UK (NICE) NICE DSU: CHTE2020 (2020) [453] and NICE DSU TSD 18 (2016) [454]

Method	Purpose	Requirements/Assumptions/Limitations	Reference
		A robust method when all effect modifiers have been identified and included in the adjustment model. However, the result may be biased if an effect modifier is missing,	Europe EUnetHTA D4.3.1: Direct and indirect comparisons (2022) [452] and D4.3.2: Direct and indirect comparisons (2022) [455]

CADTH = Canadian Agency for Drug and Health Technology; EUnetHTA = European network for Health Technology Assessment; HAS = Haute Autorité de Santé; HIQA = Health Information and Quality Authority; IPD = Individual patient data; ITC = Indirect treatment comparison; MAIC = Matching-adjusted indirect comparison; ML-NMR = Multi-Level Network Meta-Regression; MTC = Mixed treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = Network meta-analysis; PBAC = Pharmaceutical Benefits Advisory Committee; STC = Simulated treatment comparison; US ICER = US Institute for Clinical and Economic Review.

The scoping review identified 4 articles discussing ITC. It is likely that the low yield reflects that methods for indirect comparisons have been relatively stable for some time.

Table 37 Identified studies relating to indirect comparisons

Reference	Description of Method	Use Cases
Es-Skali and Spoors (2018) [456]	Comparison of ITC methods across jurisdictions	Indirect comparisons
Laws et al (2019) [457]	Comparison of guidelines for NMA	Indirect comparisons with multiple steps or multiple comparators
Leahy et al (2019) [458]	Incorporating single arm evidence into NMA	Comparison of single arm studies with multiple comparators
Phillippo et al (2019) [459]	Review of adjustment methods in NICE technology appraisals	ITCs for studies with differing population characteristics

ITC = Indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = Network meta-analysis.

A review of ITC guidance documents from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), EUnetHTA and submission guidelines from the UK, Sweden, Netherlands, Germany, France, Canada and Australia identified that ITC was a generally accepted methodology to demonstrate noninferiority, providing that the methodology and assumptions are justified [456]. All included agencies identified the Bücher method [460] as a preferred approach for indirect comparisons, while NICE and PBAC guidance documents also mentioned MAIC [461] and STC [462] as preferred. NICE and ZIN listed Bayesian MTC or network meta-analyses (NMA) [463, 464] as a preferred method (Table 38).

Table 38 Preferred indirect treatment comparison method across HTA agencies

Method	NICE	SMC	HAS	G-BA	TLV	ZIN	PBAC
Unadjusted ITC				No	No	Yes	
Bücher ITC method	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bayesian MTC	Yes					Yes	
MAIC & STC	Yes						Yes

Source: Es-Skali and Spoors, 2018[456]

G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; ITC = Indirect treatment comparison; MAIC = Matching-adjusted indirect comparison; MTC = Mixed treatment comparison; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; STC = Simulated treatment comparison; TLV = Tandvårds-och läkemedelsförmånsverket; ZIN = Zorginstituut Nederland.

To increase the transparency of MAIC and STC (or other IPD approaches), HAS requests that the full IPD dataset is submitted. NICE also indicate that it may request the IPD dataset to verify adjusted ITC approaches. PBAC guidelines request that IPD should be submitted, or justified when submission of IPD is not possible.

Es-Skali and Spoors (2018) state that the Scottish Medicines Consortium is more likely to accept indirect comparisons when the goal is to demonstrate noninferiority [456]. The G-BA guidelines state that the use of ITC should be restricted to situations where it is not possible to perform head-to-head trials.

Laws et al (2019) reported on guidance for NMA across 14 jurisdiction's HTA guidelines documents [457]. There were considerable differences across jurisdictions in the requirements for conducting and presenting network meta-analyses.

Comparisons where only single-arm studies are available is not well accepted by most jurisdictions [456]. The Bücher method cannot be applied to single-arm studies, and most HTA agencies do not consider unanchored or "naïve" indirect comparisons robust. While population matching methods can be applied (e.g., MAIC, STC or NMA [458]), validating such approaches can be difficult.

In a review of 268 NICE technology appraisals, Phillippo et al (2019) identified population adjustment methods for ITC were used in 7% (n=18) appraisals [459]. In many cases, comparisons were unanchored. The authors conclude that appraisal committees were cautious about population-adjusted analysis and typically looked for greater cost-effectiveness to minimise decision risk.

Non-peer reviewed evidence

Documents sourced from nine jurisdictions suggested that non-peer reviewed data could be incorporated into HTA evaluations. From five of these jurisdictions, including Australia (MSAC), these documents provided at least some guidance as to how non-peer reviewed data should be incorporated in the HTA document. The US ICER 2020-2023 Value Assessment Framework document provided guidance on the inclusion of grey literature (Table 39), as well as a link to the US ICER's 'Policy on Inclusion of Grey Literature in Evidence Reviews'.

No evidence was identified in the literature regarding the assessment of non-peer reviewed evidence.

Table 39 Methods for evaluating non-traditional evidence (non-peer reviewed data)

Method	Purpose	Requirements/Assumptions/ Limitations	Reference
Inclusion of grey literature	To supplement reviews of studies from peer-reviewed publications with data from the grey literature. This includes conference proceedings, regulatory documents, materials from other HTA groups, information submitted by manufacturers, and input gleaned from patients.	US ICER has a flexible and inclusive approach to evidence types, augmenting the rigour of RCT evidence with data from other real-world or grey-literature sources. Inclusion should be in-line with their 'Policy on Inclusion of Grey Literature in Evidence Reviews'.	USA (US ICER) 2020-2023 Value Assessment Framework (2020) [32]

HTA = Health technology assessment; RCT = Randomised controlled trial; US ICER = US Institute for Clinical and Economic Review.

Nonrandomised and observational studies

Nonrandomised studies include nonrandomised clinical trials, observational studies and trials without external controls. Such studies may arise due to the difficulties in conducting randomised trials, or because earlier phase studies are used for regulatory approval. Estimating the treatment effect of a health technology from nonrandomised

evidence is prone to bias and confounding, however HTA agencies are increasingly being asked to evaluate new technologies using nonrandomised evidence [465, 466].

Fifteen jurisdictions suggested that nonrandomised studies could be used to provide clinical effectiveness data in HTA evaluations, especially when RCT information is lacking. Ten of these jurisdictions provided at least some guidance as to how this should be reported. Seven jurisdictions, including Australia (PBAC & MSAC), reported on the importance of assessing the risk of bias and suggested possible tools to be used for this assessment (Table 40). Although NMA methodology can be used to incorporate observational data, few jurisdictions suggested this methodology for this purpose. Only NICE (England) provided detailed descriptions of specific data analysis methods, and NMA methods that could be used to combine the results from randomised and nonrandomised trials (Table 40). NICE also developed a checklist for evaluating the quality of an analysis on treatment effect using nonrandomised data (QuEENS checklist), which was based on five other checklists identified by NICE (Table 40).

Table 40 Methods for evaluating nonrandomised or observational studies

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Risk of bias (RoB) assessment			
Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)	ROBINS-I provides guidance on identifying study characteristics that may confound on the comparative treatment effect in nonrandomised studies (NRS). Evaluation of the risk of bias of NRS should be performed using the ROBINS-I risk of bias tool.	The domains identified in the ROBINS-I tool should be used to discuss the risk of bias Risk of bias should be performed for every outcome reported in the assessment. For single-arm clinical trials, the overall conclusion is very unlikely to be changed by assessing the risk of bias, and is therefore, not required.	Australia (PBAC) PBAC Guidelines (2016) [187] Europe (EUnetHTA) D4.6 Validity of Clinical Studies (2022) [467]
Grading of Recommendations Assessment, Development and Evaluation (GRADE)	GRADE can be used to evaluate the methodological quality or risk of bias of non-randomized studies and to evaluate the strength of the evidence base. The GRADE approach is an extensive method of grading the quality of scientific evidence	Two other instruments mentioned in the guidelines to assess the methodological quality of non-randomized studies are the Newcastle Ottawa Scale and the Down and Black Instrument The reasons for grading the selected evidence should be clearly reported.	Netherlands (ZIN) Guideline for economic evaluations (2016) [433] Ireland (HIQA) Guidelines for the Economic Evaluations (2020) [91]
KCE checklists for cohort studies and case-control studies	The KCE checklists were based on the SIGN and NICE checklists	Other checklists, such as the Cochrane Collaboration's Risk of Bias Tool and GRADE can also be used to assess the quality of observational studies	Belgium (KCE) KCE Process Book (2021) [435]
SIGN, NICE, GRADE and Centre for Evidence-based Medicine tools	Two readers should assess the article independently using an appropriate tool. Both internal validity and external validity should be assessed to ensure that factors other than the intervention do not influence the result (confounding).	SIGN, NICE, GRADE and Centre for Evidence-based Medicine, Oxford, have validated checklists.	Denmark (DEFACTUM) HTA Handbook (2007) [139]
Tools used by the US Preventive Services Task Force (USPSTF), or Cochrane Collaboration	Design-specific tools, including those used by the USPSTF and the Cochrane Collaboration, can be used to evaluate the methodological quality of included studies.	No single tool can evaluate all possible study designs included across all reviews.	USA (US ICER) US ICER's Methods Guide (2020) [333]
Statistical analysis methods			
Propensity Scoring (PS)	Propensity scoring, attempts to replicate randomisation by matching one or more characteristics, using a propensity score, between treated and control individuals. The PS can be used in the following ways: Matching of treated and untreated individuals Stratification into different subgroups based on PS Weighting of the probability of receiving the treatment Regression analysis with PS as a covariate	All baseline characteristics affecting the outcome and treatment are identified and the PS can be estimated using a logistic regression model.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]

Inverse Probability Weighting (IPW)	IPW models the probability of receiving treatment but not the outcome using the propensity score function. It uses the inverse of the PS to calculate weighted means for the treated and control samples.	The estimator will be unstable when the predicted treatment probabilities are close to zero. Flexible forms for the propensity score are required to ensure the model is able to produce non-linear associations.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
Instrumental Variable (IV) Approach	IVs are used to estimate causal relationship between the variable and the treatment, and through its effect on the treatment, with the outcome.	The assumptions are that the treatment effect is the same for everybody in the population and that treatment selection is not affected by the unobserved heterogeneity in the outcome.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
Regression Adjustment (RA)	RA models the outcome but not treatment selection. The treatment effects are then based on the difference between the predictions of two separate regression models for the treated and untreated samples.	There is an assumption of overlap in the set of covariates used to accurately estimate the treatment effect.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
Doubly robust methods: Combination of RA and IPW (RA-IPW)	This method combines outcome regression analysis with a model for the exposure (inverse weighting of the propensity score) to estimate the effect of an exposure on an outcome. As there are two model estimators, only one needs to be correctly specified to identify the treatment effect.	If both models are incorrectly specified, the treatment effect estimates are likely to be biased.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
Regression Discontinuity Design	A regression discontinuity design uses a threshold for a continuous variable to assign an intervention to those on one side of the threshold and no intervention to those on the other side.	There is a lack of overlap in the key variable(s) between the treatment and control groups determining the discontinuity. Thus, matching cannot be used.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
Difference-in-Difference	A difference-in-difference design uses either longitudinal data or repeated cross-sectional data taken from the same population to compare the changes over time. It allows for both group-specific and time-specific effects.	The important assumption is that there are common trends across the treatment and control groups.	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
NMA methods to combine evidence from different sources			
Network Meta-analysis (NMA)	the PBAC guidelines recommend not including NRS in a NMA. However, where NRS must be included, the results of the NMA both with and without the NRS should be presented. NMA methods include both frequentist and Bayesian.	NMA results of pairwise comparisons for each link in the network may be presented as supplementary analyses.	Australia (PBAC) PBAC Guidelines (2016) [187]
Bayesian hierarchical model for the NMA	Hierarchical models allow for adjustments accounting for systematic bias and for weighting by study design. Thus, the heterogeneity of treatment effects between-studies of same study design and across study designs can be modelled.	Summary estimates are pooled in a joint NMA by assuming that they are exchangeable. The level of uncertainty is generally greater, when compared to other approaches, because it allows for additional variability across studies by accounting for differences in study designs.	UK (NICE) NICE DSU: CHTE2020 Sources and Synthesis of Evidence (2020) [453] and NICE DSU TSD 20: Multivariate Meta-Analysis (2019) [469]
Observational studies to inform prior distributions	Observational data can be used to construct prior distributions, which can then either be used directly as the basic parameters of the NMA for randomised data or they can be down weighted by using an increased variance for the prior distribution.	If the prior distributions are used directly, and no adjustment made for any potential bias in the observational data, the results will be subject to bias. Power priors: Although it can mitigate bias in the observational data, it does not correct for it. How to	UK (NICE) NICE DSU: CHTE2020 Sources and Synthesis of Evidence (2020) [453] and NICE DSU TSD

	Power priors: may be pre-defined and fixed, or estimated from the data, and is used as a down-weighting factor for observational data. Mixture priors: a model-averaging approach where external evidence is used when data are sparse. Conditional posterior distributions are calculated separately for the randomised data and the non-randomised data, then combined using Bayes factors.	select the degree of down-weighting to be used in a bias-adjusted base-case analysis is not clear.	17: The Use of Observational Data (2015) [468]
Multi-variate NMA	A framework for evaluating multiple treatments across multiple outcome measures that are highly correlated. Will be mostly effective when the percentage of studies with missing outcomes is large	Based on the proportional hazards assumption. Often multivariate NMA will not improve the precision further, but the impact of outcome reporting bias is reduced due to an increased evidence base by not discarding studies not reporting primary outcome of interest.	UK (NICE) NICE DSU: CHTE2020 Sources and Synthesis of Evidence (2020) [453] and NICE DSU TSD 20: Multivariate Meta-Analysis (2019) [469]
Checklists for evaluating the quality of an analysis on treatment effect using NRS data			
Quality of Effectiveness Estimates from Non-randomised Studies (QuEENS)	To assess whether the methodology used to estimate treatment effect from NRS has been correctly applied.	It was based on the five checklists listed below, and can be used on its own or in conjunction with one of the other checklists	UK (NICE) NICE DSU TSD 17: The Use of Observational Data (2015) [468]
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices task force questionnaire	To assess the relevance and credibility of prospective and retrospective observational studies to inform healthcare decision making	The 33-item questionnaire was divided into two domains: Relevance – do the findings apply to the setting of interest to the decision maker? Credibility — do the study findings accurately answer the study question?	Berger et al (2014) [470]
ISPOR checklist for retrospective database studies	A checklist was developed to assist decision makers in evaluating the quality of published studies that use health-related retrospective databases	Retrospective databases pose a series of methodological challenges, some of which are unique to this data source. The checklist has 27 questions, covering the database, the study methodology, and the study conclusions.	Motheral et al (2003) [471]
Kreif et al. checklist	To critically appraise statistical methods to address selection bias in estimating incremental costs and effectiveness in CEAs that use observational data.	When addressing selection bias, CEAs do not assess the main assumptions, such as regression and matching. This checklist can raise awareness of these assumptions.	Kreif, Grieve and Sadique (2013) [472]
Good Research for Comparative Effectiveness (GRACE) checklist version 5	A validated checklist for the assessment of the quality of observational studies of comparative effectiveness and their usefulness for decision-making.	It contains questions about data and methods. The usefulness of all questions in this checklist have been validated.	Dreyer, Bryant and Velentgas (2016) [473]
Strengthening the Reporting of Observational Studies in	The STROBE initiative developed a checklist of items considered essential for the good reporting of observational studies (cohort, case-control, and cross-sectional designs). The 22-item checklist contains 18 items are	It was not Id for assessing the quality of published observational research.	von Elm et al (2007) [474]

Epidemiology (STROBE) checklist	common to all three study designs and four that are specific for cohort, case-control, or cross-sectional studies.		

CEA = cost-effectiveness analysis; DEFACTUM = Social & Health Services and Labour Market; DSU = Decision Support Unit; EUnetHTA = European network for Health Technology Assessment; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HIQA = Health Information and Quality Authority; IPW = Inverse Probability Weighting; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; IV = Instrumental Variable; KCE = Belgian Health Care Knowledge Centre; NICE = National Institute for Health and Care Excellence; NMA = Network meta-analysis; NRS = Nonrandomised studies; PBAC = Pharmaceutical Benefits Advisory Committee; PS = Propensity Scoring; RoB = risk of bias; RA = Regression Adjustment; ROBINS-I = Risk Of Bias In Non-randomized Studies of Interventions; SIGN = Scottish Intercollegiate Guidelines Network; US ICER = US Institute for Clinical and Economic Review; USPSTF = US Preventive Services Task Force; ZIN = Zorginstituut Nederland.

As part of the Horizon-2020 IMPACT-HTA program, Kent et al (2021) developed recommendations to support the appropriate use of nonrandomised evidence [475]. The findings of the literature review and workshop are summarised below:

- The use of nonrandomised evidence should be justified and the research question should be amenable to being answered using the nominated data.
- Studies should be planned prospectively and in collaboration with scientific advice from HTA agencies and regulators
- Identify risks of bias and methods to minimise this risk
- Perform extensive sensitivity analyses to understand the impact of data curation and analysis decisions or assumptions
- Register protocols prior to study conduct
- Report data, methods and results transparently, including data quality.
- Describe potential biases and overall risk of bias using a validated tool.
- Describe and quantify uncertainty

In addition, Kent et al provide the following recommendations to HTA bodies:

- Strengthen and standardise the scientific advice provided relating to the conduct of nonrandomised studies.
- Strengthen conditional reimbursement processes to ensure generation of further informative evidence after initial reimbursement decisions.
- Develop skills in the evaluation of nonrandomised studies
- Issue and enforce best practice guidance
- Support access to high-quality data by supporting efforts to set data standards and improve data linkage
- Support research into methods for nonrandomised study design and evaluation

A key limitation of nonrandomised studies, even those that are rigorously designed, is unmeasured confounding. Leahy et al (2022) and Sammon et al (2020) reported methods for quantifying bias in nonrandomised studies as a method of describing unmeasured confounding [476, 477]. Quantitative bias analysis (QBA) has been recently discussed in the context of regulators, however, does not appear to have been applied to HTA for reimbursement.

While multiple QBA methods have been developed, two common goals of QBA are:

- Provide a revised estimate of a treatment effect after unmeasured confounding is incorporated into the analysis; or,
- Estimate the extent of unmeasured confounding that would be required to alter the conclusion of the analysis (referred to as a threshold analysis).

Exploring the likely impact of unmeasured confounding on estimates of treatment effects can provide greater clarity to the decision-maker when considering nonrandomised evidence. However, QBA requires external data that describe the relationship between the confounder (that is unmeasured in the nonrandomised study)

and other patient level or aggregate data. These external data are difficult to attain and may not always be transitive with the target nonrandomised study. In the absence of external data, estimates of the association between an unmeasured confounder and other parameters may be informed by experts. Also, QBA models can be complex. Lash et al (2014) explain that increasing complexity in models can reduce transparency and raise concerns regarding credibility [478]. As the validation or verification of results is a key component of HTA, ensuring that models are only as complex as they are required to be is an important guiding principle.

Whether QBA should be routinely used in combination with the assessment of nonrandomised studies is difficult to recommend. There is little incentive for an applicant to explore possible impacts of unmeasured confounders if such an approach would negatively impact the size or certainty of the treatment effect. Equally, it may be difficult for a decision maker to accept a QBA that markedly improves the treatment effect of a health technology as the model and its derivation are unlikely to be fully available for evaluation.

Adjustments for treatment-switching

Randomised trials that permit patients to switch from one arm to the other (typically following progression) may be more acceptable to ethics committees and patients. However, applicants and decision makers may wish to establish the treatment effect that would have been observed had the switching not occurred.

Two studies describing methods for adjusting for treatment switching and recommendations for reporting results were identified by the scoping search [479, 480]. Multiple approaches exist, including the rank preserving structural failure time model (RPSFT), inverse probability of censoring weights (IPCW) and the two-stage approach described by Latimer et al (2019) [479].

Recommendations for applicants presenting methods for adjustment for treatment switching are well described in the PBAC Guidelines.

Curation of historical or external controls

For health technologies provided with regulatory approval based on uncontrolled study data (such as a single-arm trial, common in phase II studies), an approach is required to estimate the incremental benefits over an appropriate control. Several methods that can accommodate uncontrolled study data, in which a common reference arm is unavailable for an indirect comparison, have been described above. Such methods include MAIC [481] or STC [462].

However, where there are no reliable published sources for controls, it is possible to create a control arm based on alternative sources. External control arms can be derived from previous clinical studies, but also from RWD sources such as disease registries, electronic health records, or administrative databases. Methods identified during the scoping review are provided below.

Previous treatments of within-study patients

Two studies identified in the literature search, reported on the feasibility of using the previous treatments received by the same patients receiving the intervention as their own control group (Table 41).

If a single arm study is available for a HTA and there are no published outcomes data for current standard of care (either because there are no publications, or because the publications are considered not to be applicable), Hatswell et al (2020) proposes that the same patients included in the single arm study might act as their own control group [482]. They describe the use of the previous line of therapy as an appropriate control group.

One article identified 11 intraindividual comparisons (before and after comparisons) that were considered by the G-BA [483]. None of the comparisons were accepted by G-BA, primarily based on methodological limitations (Table 41).

Table 41 Studies that reported on generating a control am from previous treatment

Reference	Description of Method	Use Cases
Wagle et al (2021) [483]	Intra-individual comparisons (before/after clinical study designs)	No published outcomes for current standard of care.
Hatswell and Sullivan (2020) [482]	Generation of control arm using previous treatments of within-study patients.	No published outcomes for current standard of care.

The approach taken by Hatswell and Sullivan (2020) has several advantages over the generation of a control group from alternative, often real-world, sources [482]. Using the experience of patients in a prior line of therapy mitigates some of the confounding that may arise when comparing patients from separate studies, as comparisons are somewhat matched on demographic and disease characteristics. This approach has considerable limitations, particularly if the disease being studied is a rapidly progressing. Where IPD are not available for the prior lines of therapy (but aggregated data are), the creation of pseudo-IPD can be used, however this approach markedly increases uncertainty.

In 2014, the European Medicines Agency (EMA) and FDA licensed idelalisib for the treatment of double-refractory follicular lymphoma based on Study 101-09. This study was single arm in design, had 125 patients (of whom 72 had follicular lymphoma). No external historical data were available to estimate comparative effectiveness. Hatswell and Sullivan (2020) describes the generation of a control arm using the previous treatments of within-study patients, the generation of pseudo-IPD and the limitations to the approach [482].

Table 42 Advantages and disadvantages of generating a control arm using the previous treatments of within-study patients

Advantages	Disadvantages
Comparisons are matched on disease and demographic characteristics	Collection of outcome data is retrospective

Comparator (standard of care) is likely to be relevant and contemporary May be appropriate for chronic diseases where treatment switching occurs after loss of efficacy (where the main goal is disease management).	Diseases with rapid decline (e.g., some oncology indications), subsequent lines of therapy tend to have shorter durations of response, regardless of treatment efficacy. Comparisons of OS cannot be performed. Comparison is not pre-specified, and may be selectively applied (only used if favourable).

Source: Hatswell and Sullivan (2020) [482]

OS = Overall survival.

Historical control derived from post-progression survival of prior line of therapy

One study was identified from the literature search that investigated the feasibility of constructing a historical control arm from the published evidence of a prior treatment (Table 43).

Table 43 Generating a historical control derived from a prior treatment

Reference	Description of Method	Use Cases
Hatswell and Sullivan 2020[482]	Generation of control arm using post-progression survival from a study of a prior line of therapy	No published outcomes for current standard of care in the proposed line.

If a health technology does not include a control arm, no published evidence of an appropriate comparator is available and the key outcome of interest is OS, evidence from a trial of a previous line of therapy may be informative. By comparing PFS and OS from a trial of a prior line of therapy, an estimate of post-progression survival may be derived (Figure 27). This period represents the time that a patient could be recruited and receive the health technology of interest. The extent to which the proposed health technology OS exceeds the post-progression survival of the prior line of therapy may represent the incremental survival.

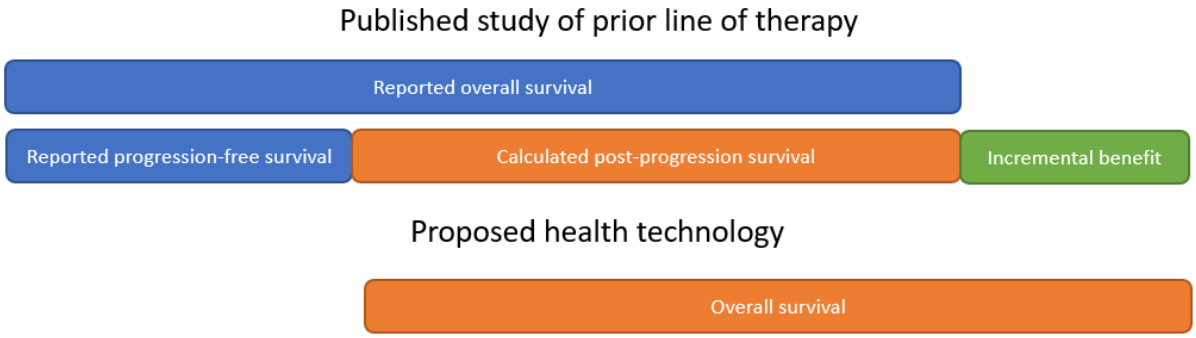

Figure 27 Using evidence from a trial of a previous line of therapy as a control

Source: Adapted from information in Hatswell and Sullivan (2020) [482]

Hatswell and Sullivan (2020) illustrates this approach for ofatumumab for chronic lymphocytic leukaemia refractory to both fludarabine and alemtuzumab [482]. As the basis for regulatory approval was an uncontrolled study (Hx-CD20-406), no control arm was available. However, the pivotal study for alemtuzumab (the prior line of therapy) presented disease-free survival and OS. Hatswell and Sullivan (2020) was able to derive

the post-progression survival curve from the alemtuzumab study, and use this as the control arm for ofatumumab [482].

Table 44 Advantages and disadvantages of using a historical control derived from a previous treatment

Advantages	Disadvantages
Can provide an estimate of incremental OS. Comparator patient population also derived from a clinical study setting, therefore likely to be more comparable than RWE (registries).	Transitivity issues associated with comparability of studies. Matching methods may be required. Requires methods to account for a delay in the initiation of subsequent therapies. If estimates are not adjusted, large delays between progression on a prior line of therapy to initiation of the health technology of interest may underestimate the incremental OS of the new treatment. Comparison is not pre-specified, and may be selectively applied (only used if favourable).

Source: Hatswell and Sullivan (2020) [482]

OS = Overall survival; RWE = Real-world evidence.

External control studies

The generation of an external controls based on RWD is methodologically challenging. Four studies considered the feasibility of using this approach (Table 45).

Table 45 Studies that reported on generating an external control based on RWE

Reference	Description of Method	Use Cases
Khachatryan, Read and Madison (2023) [484] Curtis et al (2023) [485] Sola-Morales et al (2023) [486]	Methodological considerations when generating an external control study from RWE	No published outcomes for current standard of care.
Khorchani et al (2022) [349]	Methodology for generating synthetic cohorts from aggregate or summary data	No published outcomes for current standard of care

RWE = Real-world evidence.

Khachatryan, Read and Madison (2023) provide a summary of the methodological considerations for creating and evaluating an external control study [484]. These are presented as broad concepts and are likely applicable to the comparison of any control external to the pivotal study. The considerations are summarised below:

- Outcomes in the control data should be objective and indisputable.
- The target data (population, eligibility criteria, definitions of outcomes, health care system etc) are comparable to the trial participants, definitions and settings.
- Available data captures key confounders
- Adequate information is available for the interventions (dose, frequency, duration of treatment etc)
- Notification of the regulatory agency of the intent to use an external control, and adequate details to justify the use of the approach, including source of the data and planned statistical analyses.

Khachatryan, Read and Madison (2023) concludes that, despite robust efforts to select appropriate data and analytical efforts to match patients, concerns relating to bias and unmeasured confounding may still persist [484]. Therefore, it may be inadequate to present a single approach, and multiple studies drawing on distinct data and different analytical approaches may be required to demonstrate consistency of the findings.

Curtis et al (2023) provide a list of considerations for the use of RWD to develop external controls based on the findings of a systematic literature review of the use of RWE by regulatory and reimbursement bodies [485]. The proposed considerations are high-level principles and largely support the recommendations of Khachatryan, Read and Madison (2023) [484]:

- Early engagement with regulators and HTA bodies during the planning phase.
- Consideration of the transitivity of the RWD derived controls and the intervention study.
- Ensuring adequate samples sizes.
- Transparently assess and address data quality (including data missingness).
- Selection of comparable and meaningful endpoints.
- Conduct sensitivity analyses to assess the robustness of the comparisons.

Both Khachatryan, Read and Madison (2023) and Curtis et al (2023) recommend the adoption of clear guidance for investigators, regulators and HTA agencies [484, 485], a sentiment mirrored in other studies of the use of RWD derived external controls submitted to the FDA and EMA [487-489].

Khorchani et al (2022) developed a method for generating long term observational patient cohorts (including the generation of patient-level data) where only summary level data are available [349]. The authors generated a summary table of demographic and medical parameters from a publicly available, anonymised COVID-19 cohort. The summary table included mean and standard deviation for patient characteristics. Patient and disease characteristics are correlated with the outcome (deceased or survived), and a synthetic cohort is generated. The authors compared the predicted outcomes in the synthetic cohort with the observed outcomes in the initial dataset and report a high degree of agreement. The authors state that this approach has several benefits, including over other approaches for generating synthetic cohorts.

- A synthetically generated cohort overcomes issues with recruitment that may occur for some diseases.
- Using aggregated data may avoid legal or ethical issues with privacy and sharing of data.
- This approach, which is performed using a modified random-number generation routine in R, does not require AI or machine learning, and therefore is more transparent.

The use of synthetic cohorts does not, at the moment, negate the need for data. To generate a synthetic cohort, an understanding of the correlations of patient

characteristics and outcomes is required. Therefore, a synthetic cohort, as proposed by Khorchani et al (2022), can provide greater flexibility in comparative statistics, or can be used to adjust the cohort to match a target demographic for comparison [349].

Real-world evidence

An increasing demand for faster access to effective medicines, coupled with a trend of increasing data capture has unsurprisingly resulted in an increase in the interest of using RWD for the evaluation of health technologies. The scoping review yielded 21 articles exploring the use of RWD in HTA. The scope of these articles was broad and is summarised in Table 46.

Table 46 Evaluation of RWE

Scope of included RWD / RWE articles	Citations
General overview: identifying opportunities and barriers	Akehurst et al (2023) [490] Hagen and Wisløff (2021) [491] Hampson et al (2018) [492] Liu et al (2022) [493] Roberts and Ferguson (2021) [494]
RWE for orphan drugs / rare diseases	Annemans and Makady (2020) [495]
RWE meta-analyses	Bowrin et al (2020) [496]
Use of RWE by agencies, comparison of jurisdictions	Bullement et al (2020) [497] Chan et al (2020) [498] de Pouvourville et al (2023) [499] Husereau et al (2019) [500] Kang and Cairns (2022) [501]
RWE study design and HTA / framework	Capkun et al (2022) [502] Chan et al (2020) [498] Evans et al (2022) [503] Facey et al (2020) [504] Oortwijn, Sampietro-Colom and Trowman (2019) [505]
RWD external controls	Curtis et al (2023) [485] Sola-Morales et al (2023) [486]
Re-weighting RCT evidence (applicability)	Happich et al (2020) [506]
Transferability across jurisdictions	Jaksa, Arena and Chan (2022) [507]
Biostatistical considerations when using RWD	Levenson et al (2023) [508]

HTA = Health technology assessment; RCT = Randomised controlled trial; RWD = Real-world data; RWE = Real-world evidence.

RWD are data that is derived from the use of an intervention within a non-trial setting. Analysis of these data is termed RWE. To sensibly appraise the current use and acceptability of RWE in regulatory or HTA decisions, it is important to delineate the different uses of RWE.

RWE to inform non-efficacy variables

RWE has been used, with high degrees of acceptability, to estimate model parameters such as utilisation, costs, utilities, and inform or validate model extrapolations. In a

study exploring the use of RWE in all completed NICE single-technology appraisals (STAs) from 2011 to 2018 (n=113), authors identified that 96 percent of assessments incorporated some degree of RWE. The key uses of RWE were to inform utilities (71%), costs (46%), utilisation (40%) [497].

RWE to inform efficacy

The use of RWE to estimate a treatment effect of a proposed health technology compared with standard of care is far less common. In the same study of NICE STAs, only 5% of submissions used RWE to inform the efficacy of the intervention, although nearly 18% used RWE to inform efficacy in some way. Of note, NICE rejected the use of RWE in one assessment that used RWE to estimate efficacy, noting that the historical control was nonrandomised, susceptible to bias, and not applicable to the present day [497].

While the use of RWE to inform economic evaluation model parameters remains an important consideration, the focus of this section of the report, and of the included literature, is the use of RWE to establish the effectiveness of a health technology.

Another key use of real-world data is to inform the performance of a technology that has been given provisional approval (for example, coverage with evidence development). This section of the report does not specifically address the use of RWE for the purpose of CED, however many of the findings may remain relevant.

RWE current use

Currently, RWE is successfully used to determine the appropriate comparator, natural history of the disease, treatment pathways, long-term side effects, resource use, incidence, compliance, QoL and for informing some parameters for economic analysis [490, 502]. In most cases, these uses of RWE are well established and accepted [502].

However, evidence from a scoping review indicates that there are concerns related to the use of RWE to demonstrate treatment effects [502]. Key issues with RWE included [502, 505, 509]:

- Data quality and acceptability
- Bias and confounding
- Lack of training in HTA / methods for evaluation
- Trust and transparency
- Lack of standardisation
- Transferability

RWE methods

A recent study has drawn together 41 articles from across grey literature (primarily the websites of regulatory agencies, HTA bodies, research institutes, professional and government organisations), summarised recommendations and proposed guidance [510].

The key components of RWE for use in regulatory or HTA decision making are:

- Defining the appropriate use cases
- Selecting an appropriate design and development of a protocol
- Assessing data quality of an appropriate data source
- Generating RWE using appropriate analytic methods
- Developing the report to enhance transparency and reproducibility
- Evaluation of the report

Importantly, Jaksa et al (2021) identifies current limitations in the availability of guidance to perform many of the steps of generating and evaluating RWE [510].

RWE frameworks

Several frameworks or guidance documents were identified in the scoping review. Included articles identified multi-stakeholder groups that are considering the use of RWE in HTA, including the HTAi Policy Forum [505], IMI-GetReal, RWE4Decisions, EUreccA 2025 [490], and CanREValue collaboration [498], as well as reports from individual jurisdictions [500].

In general, the use of RWE for reimbursement decisions was reported to be limited, driven by a combination of the often-poor quality of the evidence, and caution applied by payers / decision makers. Akehurst et al (2023) noted that one of the primary barriers to understanding the issues and barriers for the uptake of RWE by HTA decision makers was a lack of a clear understanding of what types of RWE could or should be used to answer what types of HTA questions [490]. RWD appears to be an umbrella term that may incorporate data derived from a range of sources, including observational studies, clinical registries, surveys, electronic health records, administrative databases or wearable technologies. While each of these methods of data collection may assist in HTA decision making, not all data sources will be suitable for answering all HTA questions. Consequently, Husereau et al (2019) has noted that an appropriate definition for RWD and RWE is required [500], and Akehurst et al (2023) has extended this to call for a taxonomy in which RWD sources and methods to generate RWE are paired with HTA questions to which the RWE would be acceptable to answer [490].

RWE across jurisdictions

Several articles were identified that discussed the use or acceptability of RWE within specific jurisdictions or across jurisdictions.

Bullement et al (2020) reported on the use of RWE in NICE assessments of cancer drugs [497]. The article reports that, across 113 identified single technology appraisals from 2011 to 2018, 96 percent included some form of RWE. This finding underscores the concern regarding the imprecision of what is being referred to as RWE and what RWE is being used to estimate. The report identifies that the most common use of RWE was to inform health-related quality of life (HR-QoL), costs and resource utilisation. Such uses of RWE have historically been well accepted by HTA agencies, however, have typically been referred to as preference studies or costing studies rather than the imprecise

umbrella term of RWE. The article does note that RWE was used in some appraisals to inform the efficacy, either of the comparator or of the intervention, however this application of RWE was less common and the precise details of how RWE was used (whether in combination with more robust evidence or as a sole source of efficacy data) is unknown. Furthermore, no link between the final recommendation by NICE and the use of RWE for specific purposes could be reported.

One article compared the use of RWE in the 'postlaunch' phase across 5 European jurisdictions [499]. The study found that HTA bodies from Germany, France, Italy, Sweden and the UK acknowledged the relevance of RWE to address postlaunch uncertainties. Currently, in Germany, the G-BA can require the pharmaceutical company to collect routine practice data for exceptional circumstances (orphan drugs etc), including non-randomised comparative studies for the benefit assessment. IQWiG is involved in the development of the data collection and analysis, and assesses the study protocol and statistical analysis plan provided by the pharmaceutical company. This difference may be attributed to differences in the listing process, where Germany seeks to confirm the value of a technology post-listing, whereas other jurisdictions tend to rely more on establishing value at the point of listing and use RWE to confirm the expected performance or as part of managed entry arrangements. Other HTA jurisdictions recognise that data collection for the purpose of coverage with evidence development or managed entry agreements is sometimes necessary. Importantly, the article notes that it is difficult to measure whether the collection of RWD as a condition of reimbursement has any impact on HTA decision making as agreements are usually confidential and RWE outcomes are rarely published, RWE is usually not the sole source of information collected prior to reassessment, and RWE may not be the sole requirement of a post-launch contract. The uncertainties associated with the collection of data in a CED process are likely to be qualitatively different to those associated with the use of RWE for the initial submission's estimate of clinical effectiveness.

One theme identified in the article, that may limit the development of clear or definitive guidelines regarding the acceptable use of RWE, was that the credibility of RWE (and the data sources from which the RWE was developed) need to be established individually. This concern was raised because data sources and collection methods are not always transparent [499].

Key barriers to the use of RWE

Many articles outlined barriers to the use of RWE for informing effectiveness. Primary amongst these barriers were technical (availability of good quality RWD) but also acceptability. In one study [500], the authors described large disparities across Canadian provinces in terms of access to relevant data, and they link this to governance models and funding. However, even if RWD are available, it remains unclear whether HTA agencies would find RWE acceptable to be used as the primary source that informs a reimbursement decision because the generation of RWE is rarely transparent, and data quality remains a concern [499, 502, 505, 509].

Information outside of clinical studies

HTA Agency websites from the included jurisdictions were searched to identify specific methods for the following purposes:

- identifying the patient pathway (treatment algorithm)
- identifying / monitoring long term adverse events

The specific methods that were identified are summarised below.

Patient pathways

Five jurisdictions discussed the importance of having a treatment or care pathway so that the medicinal product being assessed can be correctly placed in the treatment pathway. Three of these agencies, including Australia (PBAC and MSAC), provided guidance as to what kind of information should be sought when constructing these pathways. All three jurisdictions recommended that a literature review of relevant published clinical management guidelines be conducted to identify relevant guidance to construct the pathway. One jurisdiction suggested that, in the absence of suitable treatment guidelines, an expert panel and/or a well-designed survey should be used to inform the pathway (Table 47). Consideration should be given to the inclusion of patients and patient groups in the derivation of treatment pathways, particularly for less well studied diseases or conditions for which the treatment landscape is variable or changing.

Long term safety

Nine jurisdictions suggested that additional information, beyond RCTs should be sought when reporting on safety (Table 47). The guidance notes that RCTs are usually too short, and the trial may be too small to capture late-onset and rare adverse events. However, six jurisdictions provided no guidance as to where this information may be sourced. Two jurisdictions, including Australia (PBAC and MSAC), suggested that a literature search that included non-randomised and registry data, and a request for periodic safety update reports, pharmacovigilance studies, case reports and/or other grey literature sources should be undertaken to capture late-onset and rare adverse events.

Table 47 Methods for capturing information outside of clinical studies

Method	Purpose	Requirements/Assumptions/ Limitations	Reference
To construct patient care or treatment algorithms			
A literature review of relevant published clinical management guidelines	To construct a flowchart showing the current clinical management of the target population and a second flowchart showing the changes arising from the proposed medicine using standard of care outlined in the clinical guidelines	May not be relevant to country in which the proposed drug is being evaluated. The current comparators may be country-specific. EUnetHTA considers that flowcharts are illustrative in reporting management pathways and requires a narrative description of the pathway.	Australia (PBAC) PBAC Guidelines (2016) [187] UK (NICE) NICE HTA manual (2022) [27] Europe (EUnetHTA) HTA Core model Version 3.0 (2016) [136]

Clinical experts An expert panel and/or a well-designed survey	An expert panel and/or a well-designed survey could be used to construct a pathway when clinical management guidelines are unavailable.	Pathways may differ or diverge from guidelines or between experts.	Australia (PBAC) PBAC Guidelines (2016) [187] UK (NICE) NICE HTA manual (2022) [27]
To identify long term adverse events not captured by RCTs			
The inclusion of non-randomised and registry data, periodic safety update reports, and/or pharmacovigilance studies	A broader assessment of harms is undertaken as RCTs are usually of short duration with strict inclusion criteria and may not capture serious adverse reactions that might occur in the long term or rarely.	The safety profile, in terms of rare and serious adverse events, may be better understood for the main comparator. This assessment should not be used to claim superior safety when compared with the nominated comparator	Australia (PBAC) PBAC Guidelines (2016) [187] USA (US ICER) 2020-2023 Value Assessment Framework [32]
The inclusion of grey literature sources	A systematic literature search is required in the assessment of harms. A broad range of study types, including observational studies and case reports, can provide additional evidence on the type, severity, and frequency of harms relevant for the assessment.	Grey literature sources include, disease or technology monitoring registries of patients receiving treatment, pharmacovigilance data and periodic safety update reports. Safety reporting in RCTs is often inadequate because rare adverse effects and those with a longer latency period are not usually detected.	Europe (EUnetHTA) HTA Core model Version 3.0 (2016) [136]

EUnetHTA = European network for Health Technology Assessment; HTA = Health technology assessment; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; RCT = Randomised controlled trial; US ICER = US Institute for Clinical and Economic Review.

SURROGATE ENDPOINTS

A surrogate endpoint is defined as a marker that is not itself a direct measurement of clinical benefit but is known to predict clinical benefit, or final outcomes, such as survival or HR-QoL [511]. Ideally, HTA decisions should be based on RCTs that report on final outcomes [512], however regulatory agencies have approved the use of technologies on the basis of surrogate endpoints. The FDA has published a table of approximately 60 different surrogate endpoints (sometimes relevant to multiple indications) that have been used in drug development programs for drugs that have received FDA approval. The table contains surrogates deemed acceptable for traditional approval and for accelerated approval (Table 77, Appendix 4).

While the use of surrogate endpoints, such as duration of response for oncology treatments, may be adequate for regulators to establish a positive benefit-risk profile, the evaluation for reimbursement decisions based on such surrogate endpoints is challenging.

Regulators are concerned whether, on balance, a new treatment will provide a benefit compared with an agreed comparator. Under this circumstance, a surrogate endpoint that is known to impact (in the same direction) on final outcomes may be adequate to conclude benefit. However, HTA agencies are required to consider the value of a treatment. Therefore, it is not just the direction of the relationship between the

surrogate endpoint and the final outcome that is important, but also the magnitude or quantification [513, 514]. Applicants or sponsors requesting reimbursement may also prefer their technology to be assessed for improvements in survival and QoL, rather than truncating value assessments to earlier, less patient-relevant endpoints. To estimate the impact on final outcomes, surrogate endpoints must be validated and translated.

As the use of accelerated regulatory approvals is increasing, the number of technologies listed based on surrogate endpoints may also increase. Where such an approach deprives HTA of evidence of the impact on final outcomes, methods for evaluating surrogates are required to establish the value of a new technology.

HTA reimbursement decisions based on the translation of surrogate endpoints to final outcomes are less certain than those based on observed final outcomes. The uncertainty relates to the validity of the translation of surrogate endpoints to final outcomes, and the risk is that the value assessment is over- or underestimated. Therefore, in the presence of evidence supporting the treatment effect of a technology that includes final outcomes (i.e. patient-relevant outcomes), assessments of surrogate endpoints should be avoided, or only included as supplementary analyses. However, there are cases where the use of surrogate endpoints may assist the value assessment of a technology (Table 48). For all use cases in the table below, it is assumed that the surrogate outcome can be validated.

Table 48 Use cases for surrogate endpoints in HTA decision-making

Decision	Possible Use Case	Conditions
Definitive	Claim of noninferiority supported by equivalence in surrogate endpoints	Comparator has been approved on the basis of final outcomes The relationship between the surrogate outcome and final outcome is well established or future evidence of final outcomes of the proposed technology is pending
Definitive	Surrogate endpoints are used in support of robust final outcomes evidence.	Surrogate endpoints are not used to provide the estimate of treatment effect in clinical or economic assessments.
Provisional[a]	Technology provided accelerated approval by regulators, and evidence of the effect on final outcomes is pending.	The translation of surrogate endpoints to final outcomes is validated and transparent. Where there are limitations to the translation of surrogate endpoints, steps are taken to mitigate risk of inaccurate estimates.
Provisional[b]	No final outcomes evidence is pending and not likely to be studied. Coverage with evidence development, or post-reimbursement data collection, will be required.	Data collection can be designed to capture treatment effect, and/or verify the surrogate relationship. Where there are limitations to the translation of surrogate endpoints, steps are taken to mitigate risk of inaccurate estimates.
Definitive	The effect on final outcomes based on the translation of surrogate outcomes is supported by multiple sources of evidence, and risks associated with extended extrapolation of treatment effects is mitigated.	The translation of surrogate endpoints to final outcomes is validated and based on multiple sources of evidence. The risk of inaccurate estimates generated by the use of surrogate measures to predict very long-term outcomes is mitigated.

[a] subject to agreement to provide updated data in a timely manner and reassessment of value based on final outcomes.

[b] subject to agreement to collect observational data and reassessment.

HTA = Health technology assessment.

The scoping search identified two articles that discussed the use of surrogate endpoints in HTA. The small yield indicates that many methods for the validation of surrogate endpoints were developed prior to the literature search period. However, multiple other included articles mention the use of surrogate endpoints for specific use cases, such as for ATMPs.

Grigore et al (2020) presented a survey of methodological guidance for the use of surrogate endpoints across international HTA agencies [360]. It identified that, of the 73 HTA agencies surveyed, 29 (40%) presented methodological guidelines that referenced surrogate endpoints. Most European HTA agencies have adopted the principles of handling surrogate endpoints as published in 2015 by EUnetHTA [515]. However, the UK (NICE), Germany (Institute for Medical Documentation and Information, and IQWiG), Australia (PBAC), and Canada (CADTH) developed more prescriptive requirements for the validation of surrogates.

Weir and Taylor (2022) reviewed how HTA reimbursement agencies use evidence based on surrogate outcomes, and recommended additional steps to support the use of surrogates [514].

To present the current state of art of the use and evaluation of surrogate endpoints in HTA, additional articles were pearled from the included methods papers.

Current methods for incorporating surrogate endpoints into HTAs, as described by HTA agencies, were summarised by Grigore et al. The process described by PBAC and MSAC appeared to be more comprehensive than most other HTA agencies. For those agencies that described the approach to the use of surrogate endpoints in assessments, the key components were similar:

1. Establish a biological rationale for the relationship between the surrogate and the final outcomes (MSAC – additionally, support this through epidemiological evidence).
2. Quantify the relationship between the surrogate outcome and the final outcome using randomised trial evidence (of the same and/or different class of technologies), or meta-analyses.
3. Explain why the relationship between the surrogate outcome and final outcome observed in the evidence is applicable to the proposed technology. In some cases, HTA agencies have stated that validation should be considered as technology specific.
4. Quantify uncertainties in the evidence.
5. Justify the extrapolation of a surrogate to final outcome relationship to a different population or technology of a different class (or different mechanism of action).

In general, the approaches used by International HTA agencies are either similar or less prescriptive than the approaches described in the PBAC and MSAC Guidelines. However, IQWiG (Germany) additionally provide acceptable cut-off values for the measures of

association between surrogate and final outcomes, stating that the lower bound of the 95% interval must include a correlation coefficient (r) ≥0.85, or a regression-based model R^2 ≥0.72. Grigore et al recommend that HTA agencies provide explicit guidance for the use of surrogate evidence in HTA where evidence incorporating patient-relevant endpoints is lacking.

Methods for the validation of surrogates are well described in the literature, and typically follow the approaches described by the current MSAC and PBAC Guidelines. Ciani et al (2017) summarises the validation approach as establishing biological credibility, establishing a relationship between the surrogate and outcome at the cohort or individual patient level, and/or evidence from several clinical trials of correlation between treatment effects on the surrogate and final outcomes [511]. Their approach involves three steps:

1. Establish the level of evidence supporting the relationship between the surrogate endpoint and the final outcome
    a. Level 1 relates to RCTs showing that changes in the surrogate endpoint result in commensurate changes in the final outcome
    b. Level 2 relates to a consistent association between the surrogate endpoint and final outcome (from observational studies)
    c. Level 3 relates to biological plausibility of a relationship between the surrogate endpoint and the final outcome
2. Assess the strength of the association
    a. Undertaken using a meta-analysis of all RCTs
    b. Report on the association between the trial level surrogate and final outcome and on the patient-level treatment effect of the surrogate and final outcomes
    c. Report the correlation coefficients.
3. Quantify the relationship between the surrogate and final outcomes
    a. Estimate and apply a surrogate threshold effect (the size of the change in the surrogate that is large enough to produce a clinically meaningful effect on the final outcome).

After describing a range of methods for considering surrogate endpoints, Weir and Taylor conclude with suggestions for future attention. Three key points relevant to HTA decision-making are presented below [514].

1. Consider methods (such as quantitative decision analytic frameworks) that ensure the transparency of the quantification of the surrogate to final outcome relationship. Use robust methods to establish the relationship.
2. Avoid the use of non-validated surrogates and limit the use of evidence based on validated surrogates to where expedited evaluation is necessary (e.g., diseases that have high unmet clinical need).

3. Increase the use of conditional models of reimbursement where therapies provided with provisional approval are reassessed using confirmatory trials based on final patient outcomes.

VALUE FRAMEWORKS AND MULTIPLE CRITERIA DECISION ANALYSIS

The assessment of value in HTA differs across jurisdictions but may be broadly divided into comparative clinical benefit assessments, economic evaluations and value based assessments. These different value assessments represent increasing scopes or perspectives, with clinical benefit solely informed by the effectiveness of a technology (similar to regulatory assessments), economic evaluations informed by cost-effectiveness and broader value-based assessments incorporating other aspects of value.

At each step, there is variation in what parameters are included in the analysis and how they are considered by decision-makers. Categories of value elements are presented in Figure 28, below.

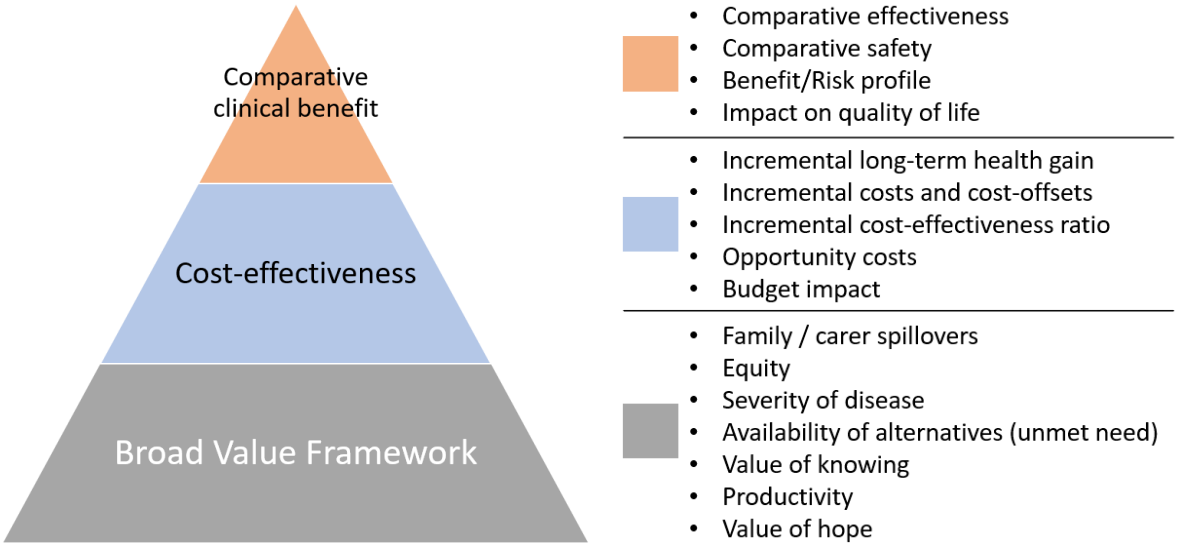

Figure 28 Narrow to broad value frameworks, with increasing number of value elements

Source: Generated for the purpose of this report.

The Australian PBAC Guidelines state that the factors that influence decision-making are broader than effectiveness and cost-effectiveness, and incorporate equity, clinical need, severity of the condition, public health issues and 'any other relevant factor that may affect the suitability of the medicine for listing on the Pharmaceutical Benefits Scheme (PBS)'. In this sense, the PBAC can be considered as taking a value-based assessment, albeit incorporating broader value domains qualitatively rather than quantitatively.

The concept of value frameworks was frequently referenced across the literature identified in this scoping review. Of the 142 articles included in the scoping review, more than one third mentioned the term "value framework" or "value assessment framework" somewhere in the study. The main areas of focus for a large proportion of these articles were MCDA methods, special populations / rare diseases, or special technologies.

The following articles were identified as specifically discussing value frameworks or MCDA methods.

Table 49 Articles discussing value frameworks

Description of the value framework	Use Case	References
Discussion of the US ICER's value framework	All technologies	Angelis, Kanavos and Phillips (2020) [516]
Value framework	Cell and gene therapies	Coyle et al (2020) [517]
Value framework	Precision medicine	Faulkner et al (2020) [518]
Value framework	Patient experience	Inotai et al (2021) [519]
MCDA	Upper-middle income countries	Jakab et al (2020) [520]
MCDA	Rare diseases	Zelei et al (2021) [521]
MCDA	All technologies	Angelis et al (2020) [522]
MCDA	All technologies	Angelis (2018) [523]
MCDA	Systematic review: All technologies	Baltussen et al (2019) [524]
MCDA	Systematic review: Oncology	Campolina et al (2022) [525]
MCDA	For determining ranking of unmet need of populations and conditions	Cleemput et al (2018) [526]
MCDA	Orphan drugs	de Andres-Nogales et al (2021) [527]
MCDA	Critique of quantitative MCDA	DiStefano and Krubiner (2020) [528]
MCDA	All technologies	Howard et al (2019) [529]
MCDA	Systematic review: Orphan drugs	Friedmann et al (2018) [530]
MCDA	Commentary for the use of MCDA in the French HTA process	Ghabri, Josselin and Le Maux (2019) [531]
MCDA	Systematic review: all technologies	Kolasa, Zah and Kowalczyk (2018) [532]
MCDA	Scoping review: orphan drugs	Lasalvia et al (2019) [533]
MCDA	Commentary for the use of MCDA in HTA: all technologies	Marsh et al (2018) [534]
MCDA	Systematic review: all technologies	Oliveira, Mataloto and Kanavos (2019) [535]

MCDA = multiple criteria decision analysis; US ICER = US Institute for Clinical and Economic Review.

Value Frameworks

A value framework is a set of explicitly stated criteria, and methods or processes to consider the criteria, to elicit the value of a health technology. In recent times, the concept of a value framework tends to refer to a framework that is broader than effectiveness and cost-effectiveness. Modern value frameworks consider the perspectives and preferences of multiple stakeholders, including patients, clinical groups, payers, and citizens.

Value frameworks that are developed to score individual value elements, particularly if those are then aggregated, are likely to be referred to as multiple criteria decision analysis methods. These are discussed in 0.

Value framework for ATMPs

The literature proposes that some treatments may require the consideration of additional value domains to better capture the effectiveness, for example, ATMPs [536]. Included studies argue that potentially curative therapies with lasting durable outcomes offer additional value elements, and therefore the following value elements may be considered [517, 537-540]:

1. Severity of disease
2. Value of hope (meaning the value of having the choice among treatments with a different balance of risks and benefits)
3. Future scientific benefits and scientific spillovers
4. Insurance value
5. Benefits associated with a non-chronic treatment (curing a disease)
6. Unmet clinical need or lack of effective alternatives

While these elements are not necessarily unique to ATMPs, multiple articles note that ATMPs are at least qualitatively different from other treatments in terms of some of the additional value elements [536, 537, 541]. A review of assessments of ATMPs in England, Scotland and the Netherlands identified that reports commonly cited key issues related to social and organisational domains. Value elements associated with organisational concerns tended to have a negative impact, while those associated with social concerns were almost entirely positive. This signals that the HTA agencies included value elements beyond effectiveness and impacts on the health care system [542].

Value framework for precision medicine

Faulkner et al (2020) reports that increasing knowledge of biomarkers and improvements in testing will continue to change the management of individual patients [518]. This increasing complexity of treatment algorithms both increases decision complexity and decreases the quality of the evidence available to make such decisions due to the reduction in the size of patient cohorts. Faulkner et al (2020) identify key elements that should be considered in the development of a value framework for precision medicine, however, they do not propose a specific framework [518]. Such considerations include:

- Validation of individual biomarkers or algorithms
- Establishment of number needed to test
- Implications for incidental findings (of diseases / risk factors not anticipated by the test)
- Ethical considerations associated with the test
- Potential for the test to identify multiple biomarkers

- Potential to identify treatments that have not been proven in the specific indication
- Cost impacts as number of biomarkers increase
- Value of the precision mechanism in increasing efficiency of pathways
- Health system effects beyond clinical and economic metrics

While Faulkner et al (2020) describe characteristics of precision medicines that should be considered during evaluations [518], the Australian approach to considering genetic and genomic testing already capture many of these considerations. It remains unclear whether the challenges associated with the HTA of precision medicine relate to the application of the current value framework, or whether the challenges are more related to a lack of data. While a broader framework, that incorporates patient perspectives and value of knowing, may be beneficial to consider, these aspects of a value framework are not unique to precision medicine.

Value Frameworks incorporating patient experience

Inotai et al (2021) performed a systematic literature review to identify how patient experience is currently captured by the HTA process, and convened an expert group with HTA experts and patient representatives, to develop value domains to capture the patient experience [519]. The proposed value domains were provided to a panel of international payer experts to help develop recommendations for implementation. Following the feedback from the external payer panel, the final five patient experience domains were:

1. Response to patients' individual needs
2. Patient and caregiver reported outcomes
3. Household's financial burden
4. Improved health literacy and empowerment
5. Improved access for vulnerable patients

These proposed components to a value framework could be applied across all technologies. However, improved health literacy and empowerment appears to be less related to the characteristics of a technology, and more related to the process of HTA and committee deliberation / communication.

The US ICER Value Framework

In 2020, the US ICER sought consultation to update its value assessment framework. A key goal of the consultation process was to assess possible methods for integrating the benefits of a technology with other contextual considerations when assessing value and making such an approach more explicit.

Following consultation, the US ICER decided against the use of quantitative MCDA methods. The US ICER stated that it had attempted formal MCDA with its committees in the past and found the technique too complicated for reliable use, and it does not

believe that the methods for weighting individual elements are adequately robust to add reliably to value judgements [32].

Rather than a formal quantitative MCDA method, the US ICER has chosen to adopt an approach that combines an established value assessment process using comparative effectiveness, cost-effectiveness and budget impact, with a process that elicits broader value elements. These broader value elements are categorised as "Other Benefits or Disadvantages" and "Contextual Considerations".

The conceptual structure of the US ICER Value Assessment Framework is shown in Figure 29.

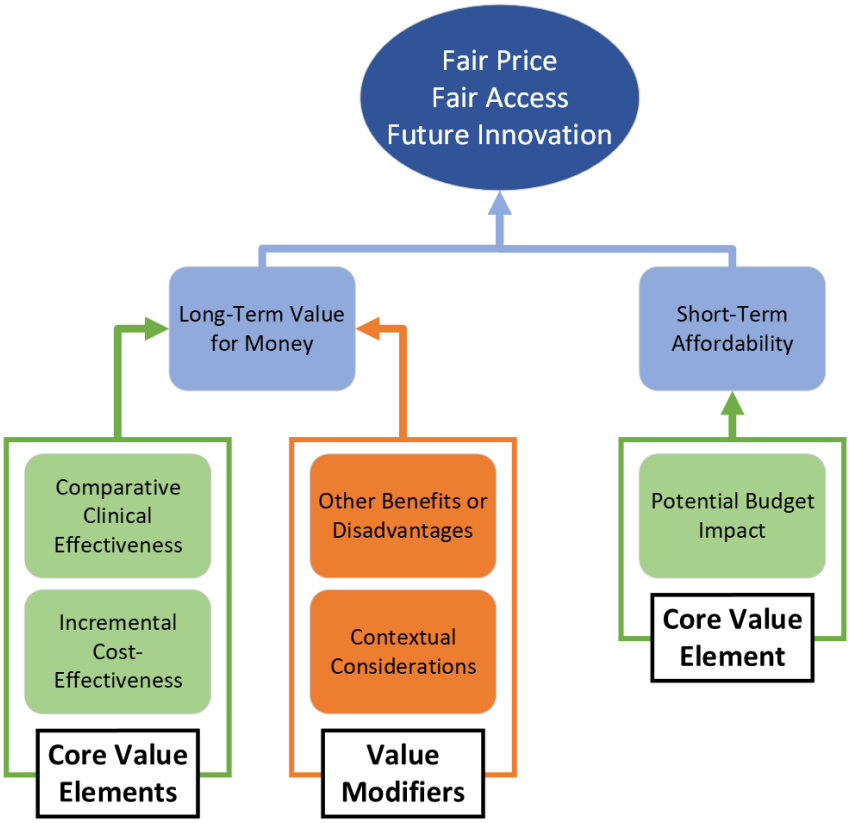

Figure 29 Conceptual structure of the US ICER Value Assessment Framework

Source: Adapted from Page 4 of US ICER 2020-2023 Value Assessment Framework [32]

The US ICER approach to value assessment is similar to that of PBAC, in that it explicitly considers comparative clinical effectiveness, incremental cost-effectiveness ratio (ICER) and budget impact, as well as other relevant factors. However, the updated US ICER value framework is more explicit regarding those other relevant factors, and also more systematic regarding how the factors are incorporated into decision-making. For most technologies, there are eight additional factors (there are minor adaptations for single- and short-term therapies and treatments for ultra-rare diseases).

During deliberation, the committee is asked to individually rate the following contextual considerations and other potential benefits or disadvantages (see Table 50 below).

Table 50 The US ICER's value framework to inform decision-making

WHEN MAKING JUDGEMENTS OF OVERALL LONG-TERM VALUE FOR MONEY, WHAT IS THE RELATIVE PRIORITY THAT SHOULD BE GIVEN TO ANY EFFECTIVE TREATMENT FOR [CONDITION], ON THE BASIS OF THE FOLLOWING CONTEXTUAL CONSIDERATIONS:					
	Very Low Priority	Low Priority	Average Priority	High Priority	Very high priority
Acuity of need for treatment of individual patients based on the severity of the condition being treated					
Magnitude of the lifetime impact on individual patients of the condition being treated					
Other (as relevant)					
WHAT ARE THE RELATIVE EFFECTS OF [TREATMENT] VERSUS [COMPARATOR] ON THE FOLLOWING OUTCOMES THAT INFORM JUDGMENT OF THE OVERALL LONG-TERM VALUE FOR MONEY OF [TREATMENT].					
	Major Negative Effect	Minor Negative Effect	No Difference	Minor Positive Effect	Major Positive Effect
Patients' ability to achieve major life goals related to education, work, or family life					
Caregivers' QoL and/or ability to achieve major life goals related to education, work or family life					
Patients' ability to manage and sustain treatment given the complexity of regimen					
Society's goal of reducing health inequities					
Other (as relevant)					

Source: US ICER 2020-2023 Value Assessment Framework [32]

QoL = Quality of life

Once the committee has considered the merits of contextual considerations and other benefits or disadvantages, they consider whether the results of the committee's assessment would impact the price at which the technology would be considered cost-effective.

The US ICER does not report a single threshold for establishing the cost-effectiveness of a technology. Instead, the US ICER proposes a price range, called the health-benefit price benchmark, which is the price of a health technology that results in an ICER of USD100,000 – USD150,000. The committee then applies the impacts of those contextual considerations or benefits/disadvantages to influence whether the maximum price of a technology should be toward the top or toward the bottom of the range (or possibly beyond the range). They do this by considering whether the other benefits or disadvantages and contextual considerations point toward a relatively lower or higher longer-term value for money.

While the impact on the acceptable cost-effectiveness ratio is not quantified or pre-determined based on the committee's thoughts of additional factors, the process is

nonetheless explicit in that it reports the factors considered, and reports the committee's ratings.

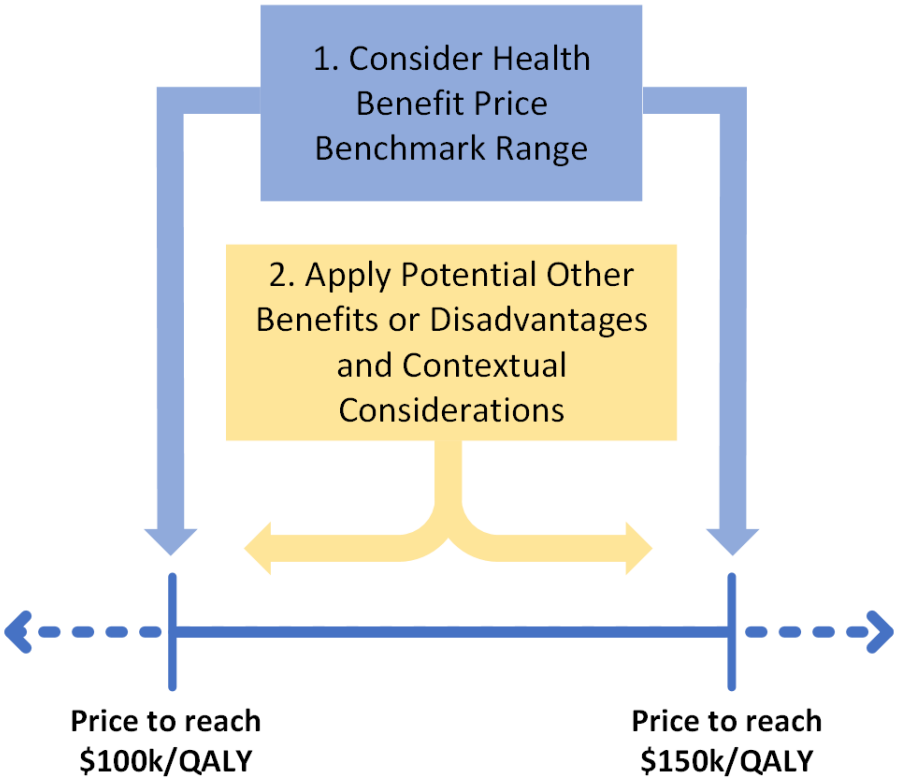

Figure 30 Conceptual guide to the application of "Potential other benefits or disadvantages" and "Contextual considerations" to judgements of value

Source: Adapted from page 34 of US ICER 2020-2023 Value Assessment Framework [32]

QALY = quality-adjusted life years.

It is noteworthy that the approach of using other relevant factors to adjust the cost-effectiveness range as applied by the US ICER is similar in some ways to the approach taken by NICE. However, while the impact of additional elements on the cost-effectiveness range is not explicitly quantified by the US ICER, NICE use a combination of non-quantified modifiers (called structured decision making) and quantified modifiers (or decision rules) (Chapter 6 of NICE Health Technology Evaluations: the manual [27]). Non-quantified modifiers may influence where cost-effectiveness is determined in the range of GBP20,000 – GBP30,000 and include the consideration of additional health benefits (not captured in the ICER), nonhealth objectives of the NHS (nonhealth benefits, equity), and innovation. Quantified decision modifiers or rules include applying greater QALY weights to populations with severe disease, measured as a QALY shortfall, and QALY weights to populations receiving highly specialised technologies that experience large incremental QALY gains.

MCDA

Angelis, Kanavos and Phillips (2020) report that broader value elements are considered by most HTA agencies around the world, but that the role and impact of these factors

on decision-making lacks transparency [516]. They claim that variations in HTA decision-making, as might be driven by differences in the consideration of other value elements, could have implications on efficiency and fairness. The authors claim that one method to increase the transparency of the incorporation of broader value elements into decision-making, and improve consistency of decisions, is to apply MCDA, or multiple criteria decision analysis.

The scoping review identified a large number of articles that discussed the use of MCDA in the HTA process. As an MCDA model typically represents a quantitative approach to value assessment, it is expected that this approach will also be addressed by other Review Questions more aligned with economic analysis. However, a brief summary of MCDA is provided here.

Definitions

There are several definitions of MCDA in the literature. An early definition by Keeney and Raiffa (1993) defined MCDA as "an extension of decision theory that covers any decision with multiple objectives [543]. A methodology for appraising alternatives on individual, often conflicting criteria, and combining them into one overall appraisal." Belton and Stewart (2002) defined MCDA as "an umbrella term to describe a collection of formal approaches, which seek to take explicit account of multiple criteria in helping individuals or groups explore decisions that matter" [544]. The key differences in the definitions are that Keeney and Raiffa (1993) initially required that MCDA aggregates information into a single expression of value [543].

ISPOR defines MCDA as a set of techniques that use structured, explicit approaches to decision-making based on multiple criteria, whether the approach is quantitative or qualitative [545].

Recent literature has adopted different categories of MCDA. A systematic review and consensus development process proposed three types of MCDA: qualitative MCDA, quantitative MCDA and MCDA with decision rules [524].

Qualitative MCDA

A committee deliberates on the performance of a technology by considering explicitly defined criteria. *The report proposing the category identified only one study that purported to use qualitative MCDA. A committee decision-making process based on multiple defined criteria, where no overall score is generated for a technology, may be common in committee considerations. However, it does not appear to be commonly labelled as 'qualitative MCDA'.*

Quantitative MCDA

Upon defining the criteria for use in deliberations, stakeholders preferences are used to specify a value for each criterion, and values are weighted using various methodologies. A committee / HTA agency applies a score for each of the criteria, which is then multiplied by the pre-determined weighting, and an overall score is generated for each technology (typically additive). Once multiple technologies are ranked,

committee members are able to deliberate on the ranking of the technologies and vary the ranking based on criteria that are not well captured. *This appears to be the primary type of method to which MCDA refers.*

MCDA with decision rules

The examples provided to describe MCDA with decision rules include the use of different acceptable ICERs based on disease severity (as is used in The Netherlands) or different acceptable ICERs based on criteria for rare diseases (such as is used by NICE). These described approaches deviate from typical quantitative MCDA. The use of decision rules to vary the ICER threshold is not currently applicable to the Australian setting, where no explicit threshold is applied in decision-making. *The systematic review that provided these definitions did not identify a single study that referred to "MCDA with decision rules".*

To avoid possible confusion, the use of the term MCDA in this report refers to quantitative MCDA unless otherwise specified.

MCDA used across jurisdictions

The use of MCDA was not identified in agency reports. Only one jurisdiction (NICE) used a formal weighting of benefits approach, using QALY weightings that differ from the reference case, in the decision-making process (Table 51). Details of the approach are discussed in 0.

The Canadian jurisdiction of Ontario did not endorse the MCDA approach as they decided that the structured decision making introduced undesirable rigidity into the process. Many countries used a more informal approach by taking other information, such as consumer experiences and equity issues into consideration during the decision-making process.

Table 51 Methods for weighting of benefits in decision-making

Method	Purpose	Requirements/Assumptions/ Limitations	Reference
QALY weighting	When relevant and in exceptional circumstances, an analysis that explores a QALY weighting that is different from that of the reference case can be accepted	Applying modifiers should be morally and ethically supported by reason, coherence, and the available evidence.	UK (NICE) NICE HTA manual (2022) [27]

QALY = Quality-adjusted life year.

MCDA applied to score the value of a technology

The use of MCDA in HTA does not appear to be widespread. A systematic review of MCDA methods, published in 2019[524], identified the appraisal of orphan drugs in Bulgaria [546], and the use of a priority score card in Hungary [547] as two examples of the use of MCDA.

There is considerable heterogeneity in the methods for MCDA used in healthcare decision-making. Another systematic review of MCDA methods identified 15 studies all

reporting the use of MCDA for oncology medicines [525]. MCDA models reported the use of as few as four criteria to as many as 20 criteria, however categories of criteria that were consistently addressed included effectiveness and economic impact. Scoring techniques and weighting techniques differed across studies.

An Australian study reported the development and the application of an MCDA tool to assist decision-making for health technologies in Queensland [529]. The study reported that there was considerable variation in the derivation of criterion weights across individual committee members. However, the committee reported that the use of MCDA was useful for focussing deliberations on those technologies with low scores and with large variations in scores.

A systematic review of articles applying MCDA to the appraisal of pharmaceuticals (for reimbursement) published in 2018 identified 16 articles [532]. The systematic review included 3 studies specifically addressing orphan drugs or rare diseases. As with previously described systematic reviews, the number of criteria used within the studies varied considerably, from 4 to 32. Most of the included studies developed the MCDA model criteria from the literature, though a minority did develop criteria in collaboration with stakeholders. Weighting of criteria was typically performed by patients, clinical experts, payers and the general public. The authors conclude that the 'core' benefit of MCDA as a tool for informing reimbursement is its transparency. However, the authors do not explain how MCDA improves transparency, or how transparency is defined. The authors do concede that there is a lack of consistency among the included studies and recommend the development of MCDA guidelines.

A systematic review published in 2018 reported on 129 articles that discussed MCDA methods or its use in HTA (including 46 MCDA model application studies) [535]. Although the search period was between 1990 and 2017, more than half of all identified studies were published in the most recent three years. The review also applies a tool for assessing the methodological quality of MCDA studies (called PROACTIVE-S), which reports the extent to which a study follows good practice considerations.

While the systematic review provides only high-level discussions of the included papers in terms of the MCDA methodology, it does provide a comprehensive list of challenges and limitations identified across studies.

Table 52 Challenges and limitations in published MCDA studies (n=129)

Challenge or limitation	Number of studies
Evidence and Data related Difficulties Identifying robust, comparable data to inform or score criteria. Lack of consensus of definitions of data. Sense of information loss.	47
Value System Differences and Participant Selection Issues Differences in value systems across stakeholders and countries Value systems may be influenced by small panels/committees Not clear whose views should be considered, and limitations due to sample sizes	46

Participant Difficulties Difficulties in participants interpreting data or understanding evaluation processes Inputs may be critically influenced by vested interests Language and translation barriers	33
Balancing Methodological Complexity and Resources MCDA is methodologically complex and may require time and costs for developing models Requirements for MCDA modelling may impact timeliness of several steps in the HTA process Evaluation demands are increased for both critiquing and reporting MCDA models	21
Criteria Selection and Attribute Building Difficulties The definition of evaluation criteria is time-consuming, difficult and subjective Some criteria (such as equity) are difficult to operationalise Lack of guidance on model development and number of criteria, with large numbers of criteria leading to cognitive burden	20
Uncertainty Modelling Needs HTA will identify uncertainty from multiple sources – choice of criteria, selection of categories, scoring and weighting methods. Conveying overall uncertainty will be difficult. Evaluators may not be able to identify whether weights are reasonable.	19
Model Additivity Issues Additive MCDA models may not deal with thresholds (such as a toxicity profile that is unacceptable) Criteria may not be exhaustive or mutually exclusive, so there may be double-counting and interdependencies Applying more complex methods to overcome limitations in additivity issues require more complex elicitation questions	17
Methods' Selection Issues No consensus about the best framework and weighting method – as methods are not standardised, it raises validity issues The selection of method may introduce bias There is no gold standard against which to compare results, therefore the performance of MCDA is difficult to measure	17
Consensus Promotion and Aggregation of Participant Answers There is no clear understanding of how to measure consensus, or what constitutes appropriate consensus	12
Introduce Flexibility Features for Universal / General Evaluation Models Conceptual and methodological difficulties in developing universal models, different models tend to be built for different contexts	9
MCDA Training and Expertise Needs Lack of familiarity in MCDA techniques, training is required for staff and participants	7
Model Scores Meaningfulness Issues Difficulties in the interpretation of outputs, which need to be tested and validated Scores are relative and cannot be used as a cost-value ratio Scores do not provide information on absolute effectiveness, utilities or costs	4

Source: Oliveira, Mataloto and Kanavos (2019) [535]

HTA = Health technology assessment; MCDA = Multiple criteria decision analysis.

Other than the Australian study that reported that the decision-making committee found MCDA to be useful for focussing deliberations, no included studies reported evidence of the benefits of MCDA, such as improving the quality or timeliness of decision-making. Kolasa, Zah and Kowalczyk (2018) explicitly state that none of the 16 included studies in their systematic review reported "how MCDA results actually impacted the real-life settings" and stated that there is a need for capture MCDA outcomes [532].

While the literature on MCDA does not present evidence of the benefits of an MCDA process, it does reveal that the criteria relevant for decision-making is typically far broader than comparative effectiveness, cost-effectiveness and budget impact. In many studies, these three criteria combined contributed to less than half of the overall MCDA weighting (particularly in rare diseases). Of interest, the importance of criteria differed by stakeholder, with payers tending to focus more on cost-effectiveness and patients allocating greater weight to availability of alternative treatments and impacts on daily activities [548].

As MCDA does not well incorporate opportunity costs into the decision-making framework, one option that has been proposed is to remove efficiency (i.e., cost-effectiveness) from an MCDA model. The framework then becomes a more complete measure of benefit, incorporating additional elements of value, and is considered alongside the results of an economic evaluation [534].

MCDA for orphan drugs

One study undertaken in Spain reported the development of an MCDA for the purpose of informing decision-making for the reimbursement of orphan drugs. The article argues that Spain, like most developed countries, evaluate orphan drugs using the same criteria as other medicines. However, due to their high cost and uncertainty regarding effectiveness, it is difficult to conclude cost-effectiveness, yet they note that many orphan drugs are funded nonetheless. The authors argue that this implies that criteria beyond efficiency are being taken into account. The study proposes the use of an MCDA approach to improve the transparency of the decision-making process. The MCDA project, called the FinMHU-MCDA study, used approaches based on the ISPOR guidelines for developing MCDA [545, 549].

The process involved defining criteria to be considered for reimbursement decisions for orphan drugs, which were derived from the literature and consolidated into 17 unique concepts. The criteria were shared with a panel of experts via an online questionnaire, where criteria could be modified and new criteria added. The results of the survey were shared with the panel and a consensus was reached regarding the final criteria and the levels or categorical responses to the criteria (Table 53).

Table 53 Reimbursement criteria for orphan drugs from the FinMHU-MCDA study

Criteria	Level
Population	
Number of patients affected by the disease who are candidates for treatment, according to prevalence and/or incidence	Prevalence < 0.2 per 10,000 inhabitants Prevalence between 0.2 and 1 per 10,000 inhabitants Prevalence > 1 but < 5 per 10,000 inhabitants
Age at the beginning of treatment of the disease	Nonpediatric Pediatric
Disease	
Degree to which patient is affected	Mild Moderate

	Severe
Economic impact of the disease on the health system and society in general, considering the types of resources and costs involved[a,b,c]	Low economic impact Moderate economic impact High economic impact
Treatment	
Adverse events due to treatment: Seriousness Frequency	 Serious AE Nonserious AE Frequent AE Infrequent AE
Availability of different therapeutic options	No other therapeutic options There are other options, but the current treatment improves health more than the alternatives There are therapeutic options with similar characteristics
Expected clinical benefit or actual clinical benefit in the framework of a clinical trial	High benefit: curative or significant increase in survival Moderate benefit: stabilization of the disease or improvement in QoL Low benefit: palliative or symptomatic
Credibility and robustness of evidence	Randomized controlled trial with comparator Other types of clinical trials or with inappropriate comparator Nonrandomized study
Change in patient's HR-QoL due to the treatment received, associated with impaired mobility, personal care, daily activities, pain/discomfort, or anxiety/depression	Treatment improves HR-QoL Treatment does not modify HR-QoL Treatment decreases HR-QoL
Economic evaluation	
Cost per patient per year[d]	< EUR100,000 per year EUR100,000 to EUR300,000 per year > EUR300.000 per year
Reduction in costs derived from application of treatment, including medical costs[a], non-medical costs[b], and indirect costs[c]	Avoids direct medical and nonmedical costs derived from the disease and indirect costs due to loss of productivity Avoids direct medical costs derived from the disease Does not avoid direct/indirect costs of the disease, or there is not enough information on avoided costs
Efficiency of a treatment, according to the criterion and the payers' willingness to pay, evaluated by the ICER expressed as cost per QALY gained from the intervention against a comparator or standard treatment	Cost-effective Not cost-effective

Source: de Andres-Nogales et al (2021) [527]

[a] Direct medical costs associated with the diagnosis, treatment, and management of patients with the disease

[b] Nonmedical direct costs derived from the disease (generally borne by the patient, caregiver, or social services)

[c] Indirect costs derived from the loss of productivity due to absenteeism/sick leave

[d] Cost per complete treatment in single-dose treatments

AE = Adverse event; HR-QoL = Health-related quality of life; ICER = Incremental cost-effectiveness ratio; MCDA = Multiple criteria decision analysis; QALY = Quality-adjusted life years; QoL = Quality of life.

The criteria were then weighted according to their relative importance using a preference elicitation technique (discrete choice experiment). The discrete choice experiment involved the creation of hypothetical scenarios resembling unique combinations of criteria. The scenarios were delivered in pairs, and participants were

requested to select the most favourable scenario for funding. This step involved different stakeholders invited to participate in the study (n=28). The final step involved a committee deliberation on the results of the DCE component.

The results of the study identified that the criteria with the greatest weight in the MCDA model were patient HR-QoL, efficacy, availability of treatment alternatives and disease severity.

The authors concluded that, while reimbursement decision-making is the remit of health authorities, there is great importance to include multiple stakeholders in the decision-making process for rare diseases, particularly patients and health professionals. They propose that the development of an MCDA tool is a good approach to facilitate participation across stakeholders.

A systematic review of the use of MCDA for the appraisal of orphan drugs conducted between 2000 and 2017 identified seven articles and six abstracts [530]. As was reported for MCDA for use in broader HTA contexts, there was considerable heterogeneity in the criteria used in the MCDA tools for orphan drugs, with studies applying between 3 and 16 criteria. Most studies included disease severity and clinical effectiveness, safety and cost-effectiveness.

A scoping review published in 2019 identified 11 studies that included MCDA frameworks for the assessment of orphan drugs [533]. Most included studies incorporated criteria relating to the severity of the disease, availability of alternatives or unmet need, comparative efficacy, and safety or tolerability. Criteria that were less commonly included in MCDAs (or were included but considered to have low relevance) were cost-effectiveness, budget impact, rarity of disease, use for a single indication, innovation and complexity of production.

A systematic review of articles reporting the use of MCDA and value frameworks for the assessment of treatments for rare diseases, published in 2021, identified 15 studies [521]. The review compared the criteria in MCDA tools developed specifically for orphan drugs to those in general MCDA tools that may be used but were not specifically developed for orphan drugs. The study identified that, in general, there was overlap in the most prevalent criteria. These were comparative effectiveness and safety and HR-QoL effects. However, in the orphan specific MCDA tools, criteria for unmet need and severity of disease were more prevalent (though were still present in a majority of the general MCDA tools).

The systematic review did not present a comparison of the weights across the tools, therefore it is difficult to comment on the relative importance of the criteria in MCDA specific to orphan drugs compared with general MCDA tools.

MCDA for priority setting

One article presented the use of MCDA to generate a ranking of conditions by unmet need [526]. In Belgium, some health technologies are eligible for early temporary reimbursement (ETR), which provides financial contribution to the use of health

technologies without fully determined effectiveness, safety, economic or budget impacts. To be eligible for early temporary reimbursement, a health technology must be targeted at a condition that has high unmet need. The authors used an MCDA approach to rank conditions by unmet need, by considering 5 weighted criteria relevant to therapeutic and societal need.

The MCDA process involves an evidence assessment, followed by a score that is applied by experts (the unmet needs commission) and that is then weighted by the public.

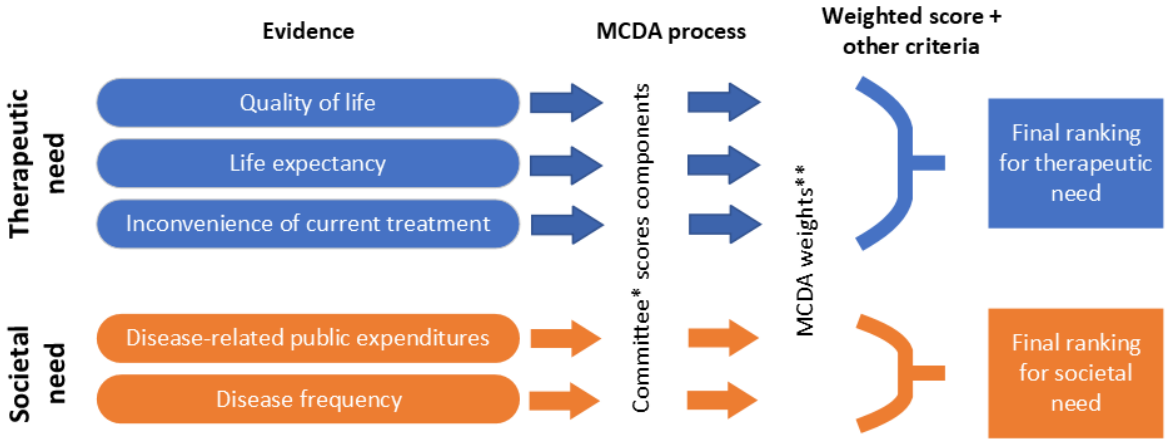

Figure 31 Conceptual MCDA process applied to the ranking of topics by unmet need

Source: Adapted from Cleemput et al (2018) [526]

*Members of the unmet needs commission; ** MCDA weights are derived from the general public.

The authors report that the approach was practical and easy to implement, and that the time investment and transparency of the methodology was acceptable to commission members. The use of an MCDA process to develop a list of priorities for health care resourcing represents a departure from the majority of the literature identified in this scoping review, which is to use MCDA to score or rank individual health technologies. The use of MCDA to develop prioritisation lists for conditions may be a reasonable mechanism for decision-makers to triage technologies into more rapid pathways for provisional approval.

Summary of MCDA and value framework findings

This Review identified two systematic reviews, a scoping study and a study of MCDA conducted in Spain. No studies reported on the performance of MCDA compared with an alternative value assessment process, or on the impact that MCDA had on decision-making.

MCDA tools used for orphan drugs or treatments for rare diseases tended to place the greatest weight on disease severity, availability of alternative treatments, efficacy and safety. While many of the included studies discussed MCDAs developed specifically for orphan drugs, it is unclear whether they are considerably different than for non-orphan drugs. The criteria with the greatest weight across MCDA models for rare diseases are the same as those for non-rare diseases. For example, the EVIDEM framework

(developed for the assessment of all drugs) reports that effectiveness, QoL, disease severity, "limitations of comparative interventions" (which is taken to mean unmet need), and quality of the evidence are the top four weighted criteria. This appeared highly consistent with the MCDAs developed for orphan drugs.

If more generic MCDA tools are largely compatible with those MCDA tools developed specifically for orphan drugs, it may be reasonable to apply generic tools for consistency of evaluation across all technologies. Limitations of using a generic MCDA tool for orphan drugs is the inclusion of cost-effectiveness and certainty of evidence criteria in many MCDA models. However, some authors have argued for the removal of cost-effectiveness from MCDA tools and the provision of cost-effectiveness analysis (CEA) alongside MCDA [534], particularly due to the risk of double-counting effectiveness and cost-effectiveness in additive models. Likewise, capturing risk associated with lower quality evidence may be addressed outside of an MCDA tool using approaches such as coverage with evidence development or pay for performance [550].

In general, the argument for application of MCDA specifically for treatments of rare diseases is not well formulated. It is variously stated that, as orphan drugs tend not to be considered cost-effective according to willingness-to-pay or ICER thresholds, a broader set of criteria are required to appropriately value these technologies [533, 546, 551]. While narrow value frameworks may not be adequate for some treatments, this argument leaves little room for the possibility that some treatments for rare diseases (as is the case for all other treatments), at a particular price, are not cost-effective.

It appears more plausible that the reasons why some drugs are not listed when they ideally should be (that is, they are priced appropriately) is either: the impacts on patients or caregivers are not well captured by traditional HTA methods; or, the threshold used to establish cost-effectiveness is not high enough. If these are the key barriers for establishing the cost-effectiveness of an orphan drug, then the solutions may be:

- Develop methods to better capture the impact of a disease on patients, their families and carers
- Vary cost-effective thresholds based on pre-determined rules informed by societal preferences

Such solutions have the benefit that the decision-making process remains similar to that for all health technologies, rather than diverging into the use of an MCDA approach for orphan drugs and abandoning a well-practiced approach.

The varying of cost-effectiveness thresholds, or applying equity weights to QALYs (which has the same effect), has been undertaken in several jurisdictions. For example, the Netherlands uses three thresholds based on disease severity, with diseases of the lowest severity required to achieve an ICER of EUR20,000 per QALY, and those with the highest severity permitted a threshold that is four times greater (EUR80,000 per QALY) [552].

Studies have identified that societies' willingness-to-pay tends to be higher for orphan drugs compared with other treatments. However, the key drivers of a higher threshold is not rarity but rather disease severity and lack of therapeutic alternatives [553].

Key findings regarding the use of MCDA for orphan drugs or rare diseases include:

- A broader value framework that is considered explicitly by decision-makers, during deliberations, is required to ensure that decision-makers include values that are not commonly identified by narrower frameworks applied in HTA. However, there may be benefits if the value framework is consistent across all technologies.
- Severity of the disease (in terms of a reduction in quality and/or length of life), should be included in a value framework
- Patient-reported outcome measures (PROMs) that are adequate to capture the impact on patients, should be included in an explicit value list.
- Treatment alternatives, or unmet clinical need, should be included in an explicit value list.
- Committee decision making should account for disease severity and unmet clinical need by adjusting up or down their expectations for a cost-effective ICER in line with societal willingness to pay.

Table 54 Benefits of quantitative MCDA and a comparison with a qualitative value framework

Benefits of quantitative MCDA	Comparison with an explicit, qualitative value framework
Alignment of MCDA with value-based health care [535]	Same benefit.
Ability to account for different stakeholder preferences [535]	Same benefit.
The consideration and justification of explicit value criteria to inform an MCDA model may increase transparency [535] and quality of decision-making.	The final weighting of different value elements is not transparent. However, transparency requires more than simply reporting a score, and should include reasons for committee decisions so that consumers can engage and respond to committee recommendations.
An explicit list of criteria, and pre-defined weights for each of the criteria, may reduce the cognitive load on decision-makers [524]. However, the committee is still required to consider multiple sources of information to populate an MCDA.	Cognitive burden of applying a value framework to a decision may be related to the complexity of the framework.
In an Australian study applying MCDA to HTA decision-making, committee members reported that the MCDA results guided their deliberations by focussing on submissions with the lowest scores and those with the greatest variability in scores [529]. MCDA may improve the confidence of committee members.	It is unclear whether a non-scored value framework would improve the confidence of the committee.

HTA = Health technology assessment; MCDA = Multiple criteria decision analysis.

Table 55 Limitations of quantitative MCDA and a comparison with a qualitative value framework

Limitations of quantitative MCDA	Comparison with an explicit, qualitative value framework

An MCDA model may require additional resources to both create and to evaluate [528, 535]. MCDA models require evidence to generate criteria and inform the preference studies which deliver the weights. These data may not be robust or available [535]. Evaluator, decision-maker and participant training may take considerable time [535].	Resources will still be required to collect data to inform value elements. However, it is likely that these elements will be informed by patient and sponsor submissions. There would be a learning curve for the committee implementing a value framework, however no specialised training would be required for the committee or evaluators.
The application of MCDA has not been fully explored [530]. The comparative benefits of MCDA remain unknown.	N/A
There are clear methodological concerns regarding the use of MCDA, such as the additive value model (which cannot accommodate overlapping criteria) [531, 535]	It is unclear whether there are methodological limitations of committees applying a qualitative value framework to decisions. Arguably, committees are already applying a value framework, but it is not explicit.
It is unclear whether generic MCDA models would be adequately responsive to individual technologies or populations, and therefore multiple models may be required. For example, MCDA models that are proposed for orphan drugs or rare diseases, where cost-effectiveness has a far lower weighting, are unlikely to be applicable to technologies for more common diseases.	The risk associated with a generic value framework is the same. However, as the use of a qualitative value framework does not culminate in an aggregated estimate of value, it is more flexible to incorporate "other" value elements.
While an MCDA approach may increase transparency and certainty, it may also affect flexibility if a committee has less room for judgement in decisions [528].	A qualitative value framework retains flexibility. If committee deliberations are adequately communicated, transparency can be preserved.
Where the criteria, scoring and weights for an MCDA model are available to sponsors, there is considerable scope for challenge should a decision-maker pass a recommendation that is contrary to the likely prediction of the MCDA model. This may be reasonable if there is inconsistency in decision-making, however it is fraught where the cause is the imprecision or inaccuracy of the MCDA tool or its failure to consider all of the factors relevant to decision-making. This may negatively impact on the independence of the decision-making committee and on the relationship between the decision-maker and the sponsor.	Regardless of the committee's approach to estimating value, there are risks associated with unexpected negative recommendations. A qualitative framework, combined with transparent reporting, may be more acceptable than a committee making a decision that is inconsistent with a model prediction.
The use of quantitative MCDA approaches may actually reduce the transparency of the decision-making process, as the MCDA output would remain inaccessible to the large proportion of people who do not have an understanding of the method. DiStefano and Krubiner (2020) argue that simply publishing the weights and scores of an MCDA tool to the public does not satisfy transparency, which requires that information is understandable and relevant [528]. They argue that transparency requires decision-makers to demonstrate respect to members of the public by providing them with information to better understand a decision and the rationale for that decision [528]. As a typical member of the public is unlikely to understand and engage with the methodology, they would be deprived the opportunity to engage, challenge or disagree with the findings. This may erode public trust in the processes for healthcare prioritisation.	The use of a qualitative value framework may be more intuitively understood by patients. However, transparency could only be achieved by appropriate reporting of committee deliberations.
The use of quantitative MCDA may also reduce the quality of decision-making, as it may oversimplify complex concepts. By fitting a technology to categories, that are then scored, weighted, and aggregated, it is likely that there is significant information loss [528, 535].	No comparison of the quality of decision making using a qualitative value framework versus an MCDA were identified.
Although it has been claimed that there are many successful applications of MCDA [523, 548, 554], it remains unclear whether MCDA methods have been adopted for routine use by any international HTA agencies [534].	Qualitative value frameworks are currently used by decision makers. Recent value frameworks are well described by NICE and by ICER.

HTA = Health technology assessment; ICER = Incremental cost-effectiveness ratio; MCDA = Multiple criteria decision analysis.

Ultimately, many of the benefits of an MCDA approach can be achieved without the additional burden on sponsors and evaluators, or loss of committee flexibility, that may accompany the use of a quantitative MCDA approach. These benefits arise from the active consideration of an explicit list of criteria by a committee, whether scored or not, in combination with high quality deliberation and transparent reporting of committee findings [528].

INTEGRATING EQUITY CONSIDERATIONS INTO HTA

Some researchers have observed that they have not been able to identify specific procedures or methods for how HTA decision makers elaborate or integrate equity considerations and other value judgements [555]. Equity seems to be regarded as something in need of protecting: unjust inequalities should be reduced or at least not introduced or compounded when choosing whether to fund a technology. Or equity is regarded as something in light of which the true value of a health technology might be higher (rarely lower) than indicated by economic evaluation. This is thought to be especially the case with, for instance, ATMPs, namely because of "the absence of data from clinical studies or RWD", with value assumptions thereby especially needing explication [9].

Seven jurisdictions indicated that equity considerations in vulnerable and disadvantaged populations were taken into account during the decision-making process. Four jurisdictions, including Australia (PBAC and MSAC) provided guidance as to how to incorporate the appropriate information into the evaluation (Table 56). No details were provided in the documents obtained from the websites of the other three jurisdictions (EUnetHTA, IQWiG, HIQA).

Australia (PBAC and MSAC) allows for a discussion of equity issues in the HTA report that may influence the decision-making process. NICE also allow for a discussion but prefers if the discussion follows recognised methods of analysing, synthesising, and presenting qualitative evidence. Two other jurisdictions allow for a discussion of equity issues as part of the 'principle of Justice' in an ethical assessment (Table 56).

Table 56 Methods for equity considerations in vulnerable and disadvantaged populations

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Discussion of equity issues	Less-readily quantifiable factors that can influence PBAC decision making include equity issues, such as age, socioeconomic status, and geographical remoteness.	Issues such as access or equity can be summarised in the HTA report. Equity issues may vary for different submissions and need to be re-evaluated case by case.	Australia (PBAC) PBAC Guidelines (2016) [187]
Qualitative research	Qualitative research can be used to explore values, preferences, acceptability, feasibility, and equity implications.	Qualitative data may be collected ad hoc or through formal studies. Formal studies should be analysed using recognised methods for	UK (NICE) NICE HTA manual (2022) [27]

		synthesising and presenting the evidence.	
Ethics: principle of Justice	An ethical framework based on the four principles is commonly used in medicine. Under the principle of Justice, the concepts of equity may be put forward in the arguments.	These arguments are incorporated into the assessment report to inform the decision-makers about any equity issues. HAS methodology choices for economic assessment presuppose a specific concept of justice.	France (HAS) Methodological guide (2013) [446] Denmark (DEFACTUM) HTA Handbook (2007) [139]

HAS = Haute Autorite de Sante; HTA = Health technology assessment; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee.

Deliberative approaches

Equity is usually regarded as a consideration that should be *deliberatively* considered by appraisal committees alongside safety, effectiveness and cost-effectiveness, whose formal analyses can fail to reflect how some groups stand to be impacted differently or unfairly disadvantaged by a funding decision. Equity is often regarded as one of numerous ethical considerations that should be deliberatively considered as part of the context of the intervention [84]. Ethical issues are "grouped with legal, social, and organizational issues and treated as contextual considerations that decision makers should be aware of" [84].

Some researchers have proposed a checklist approach to assist HTA decision makers to integrate equity considerations into their deliberations in a more comprehensive and systematic way, which might increase consistency in decision-making practice [377]. The checklist varies with HTA phase. The checklist most relevant to appraisal decision making is presented in Table 57.

Table 57 Recommendations and conclusions phase of the Equity checklist for HTA

Category	Key question	Details
Scope	Were the results synthesised using a summary table that included findings relating to inequity?	Summarized results can still include findings on disadvantaged groups.
	Do the recommendations account for the different aspects through which inequities can emerge?	For example: coverage, prevalence, uptake, access to care, etc.
	Are recommendations generalizable to all population groups?	Should some recommendations specify that they do not apply to certain disadvantaged groups? Do certain recommendations target disadvantaged groups?
	Could certain recommendations increase inequities?	Could certain recommendations heighten the barrier to access to healthcare services for particular population groups? Might certain population groups have reduced resources as a result of the recommendations? Which alternatives could be suggested?
Contextual considerations	Are there legal contexts to consider in the recommendations?	Are there legal aspects regarding certain population groups that must be taken into account?

	Are there historical disadvantages to be considered in the recommendations?	For example, specific to indigenous groups or racialized populations.
	Are there recommendations relating to a change in culture and/or the institutional system which could contribute to inequities?	Could alternatives be proposed?
Stakeholder involvement	Were all relevant stakeholders included in the scoping process? Do the methods used to involve stakeholders allow for all relevant parties to be represented?	Does the way in which stakeholders are involved impede certain population groups from being adequately represented? For example: the methods for deliberation create barriers for the participation of certain persons, capacity for transportation, level of literacy for understanding the final written product, etc.

Source: Benkhalti et al (2021) [377]

HTA = Health technology assessment.

This work built on prior work by Culyer and Bombard (2012) and work by a collaboration of ethics and health economics researchers [556, 557]. The first elaborates some key conceptual questions relating to equity and its scope in HTA, while the second presents a checklist for use by decision makers in all settings but especially low and middle-income countries (Table 58).

Table 58 Priority-setting criteria to be considered in conjunction with cost-effectiveness results

Criteria	Question
Group 1: disease and intervention criteria	
Severity	Have you considered whether the intervention has special value because of the severity of the health condition (present and future health gap) that the intervention targets?
Realization of potential	Have you considered whether the intervention has more value than the effect size alone suggests on the grounds that it does the best possible for a patient group for whom restoration to full health is not possible?
Past health loss	Have you considered whether the intervention has special value because it targets a group that has suffered significant past health loss (e.g., chronic disability)?
Group 2: criteria related to characteristics of social groups	
Socioeconomic status	Have you considered whether the intervention has special value because it can reduce disparities in health associated with unfair inequalities in wealth, income or level of education?
Area of living	Have you considered whether the intervention has special value because it can reduce disparities in health associated with area of living?
Gender	Have you considered whether the intervention will reduce disparities in health associated with gender?
Race, ethnicity, religion and sexual orientation	Have you considered whether the intervention may disproportionally affect groups characterized by race, ethnicity, religion, and sexual orientation?
Group 3: criteria related to protection against the financial and social effects of ill health	
Economic productivity	Have you considered whether the intervention has special value because it enhances welfare to the individual and society by protecting the target population's productivity?
Care for others	Have you considered whether the intervention has special value because it enhances welfare by protecting the target population's ability to take care of others?
Catastrophic health expenditures	Have you considered whether the intervention has special value because it reduces catastrophic health expenditures for the target population?

Source: Norheim et al (2014) [557]

Researchers in South Africa undertook extensive public engagement to develop and test (in simulated funding decisions) a Provisional Ethics Framework to guide both evidence

collection and appraisal decision making [95]. The Framework is essentially a checklist featuring items that include potential impacts on equity (considered in terms of a fair distribution among groups), social cohesion, patients' pain and suffering, and people's safety and security from violence. The researchers showed that it is possible to produce such a guidance document specific to a country, that it is perceived to have legitimacy in that country, and that it can enrich deliberative decision making.

Quantitative approaches

In literature reviewed for this paper, equity was sometimes mentioned as something that could be undermined by particular methodological choices in economic evaluation. For instance, Australia was mindful that including production gains in economic evaluation problematically favours people who can and choose to contribute to societal production (namely work). Germany mentioned how the use of QALYs can be problematic. The US ICER was explicit in preferring deliberative over quantitative methods for considering equity, stating that it does "not believe there are reliable methods to weight QALYs gained by patients from disadvantaged" groups [32]. In view of a lack of academic consensus, the US ICER thinks that it is "premature to seek to create a separate series of cost-effectiveness thresholds related to severity, burden of illness, or "need."", including for rare diseases [32]. But this does occur in the case of NICE and several other jurisdictions. There is a variation in practice here, and no doubt debate in the underpinning scholarship.

'Equity weights' are used when the quanta of health gained by a particular population are accorded greater value (more heavily weighted) in view of equity concerns. For instance, Taiwan debates whether to accord greater value to heath gains at the end of life. Dutch academics have advised on using equity weights, including a construct of need (or being worse off than another) called 'proportional shortfall' [92]. This refers to the proportion (expressed as a ratio) of "remaining lifetime health one stands to lose by virtue of an illness if the illness goes untreated" [82]. By contrast, Norway examines 'absolute shortfall', which is presumably expressed as a number of QALYs rather than a ratio. NICE reports that QALYs may be weighted in line with absolute and proportional shortfall. The US ICER reports both absolute and proportional QALY shortfall, but it does not use them as equity weights, only deliberatively to consider whether effectiveness or cost-effectiveness analyses may under or overvalue health gains [558]. Scotland allows the use of equity weights for QALYs when industry, clinicians or patients highlight that a group of patients may "derive specific or extra benefit", such as in the absence of "other therapeutic options of proven benefit" [559]. In Japan, an equity weight of 5% is used to favour some patient subgroups before subgroup averages are combined to determine an overall ICER [558]. An equity-based increase in the ICER threshold (such as NICE and Japan use for ultra-rare conditions) is tantamount to using an equity weight.

Some researchers have recently argued that NICE's current use of equity weights "has the effect of reducing both population health and equity-weighted population health, a fundamental problem that appears to place NICE in contravention of its principles and

obligations" [560]. (Equity-weighted population health is "a measure of each new technology's contribution to population health that takes into account the relevant equity characteristics of the patients who would benefit from the new technology and the patients whose health would be forgone if the technology is adopted" [560].) The researchers observe that NICE currently considers an equity weight for life extending treatment at the end of life through "application of a maximum weight of 1.7 to the QALY gained", though NICE is considering revising or removing this [558, 560]. Similarly, in NICE's Highly Specialised Technologies programme, NICE considers an equity weight for 'magnitude of benefit', valuing a benefit more the greater it is. Specifically, there is no weighting if 10 or fewer QALYs are gained, a weight (multiplier) of 2 if 11 to 29 QALYs are gained, and a weight of 3 if 30 or more QALYs are gained [560]. The main line of critique is that NICE uses the wrong ICER threshold to begin with, namely an ICER threshold that is far higher than empirical estimates of what it ought to be. This means that equity weighting is not going to achieve its goal, and may worsen the lowering of population health that already results from NICE using an ICER threshold that is too high. The other risk that researchers highlight is that the use of equity weights can worsen inequities if, in funding a new technology, this entails displacing a technology that is already benefiting disadvantaged populations. That is, equity weights need to apply to the health foregone on account of displaced technologies, and not solely to the health gained by new technologies. Put sharply, the researchers argue that "NICE has made no efforts to reduce its standard threshold in response to emerging empirical evidence and has not taken steps to ensure that its equity weights are applied fairly across all patients affected by its recommendations" [560]. The same critique could apply to Australia if Australia was to use equity weights in tandem with an ICER threshold (explicit or implicit) that fell below empirical estimates of what Australia's ICER threshold ought to be [561].

There is evidence that France and Germany adopt an approach that consciously departs from the use of some general ICER threshold (be it explicit or implicit).

> *In France and Germany, the HTA organizations construct "efficiency frontiers" that map the cost per benefit of each therapeutic option for a specific condition. There is no cost-effectiveness cut-off or threshold. Instead, the organizations judge whether the cost increase is proportionally appropriate for the additional benefit and compare it against other drugs for the same condition [558].*

The effect of this is to ensure that the price paid for a new medicine falls in line with how costs and benefits seem to track for medicines that treat the condition (no comparison across conditions or disease areas is possible). This may be a way of accommodating equity concerns insofar as they pertain to the condition or disease area as a whole (e.g., rare diseases).

Variants of *MCDA* that accentuate equity have been proposed as means of integrating equity considerations into decision making [562]. The technology's "impact on health

equality" would be one of the multiple criteria explicitly considered [562]. If the technology stands to reduce health inequities, then its impact can be scored as, say, "very high" along a five-point scale (ranging down to "very low") [562]. Belgium set up a 10 million Euro pilot scheme to help with "unmet medical need" [563]. Over 60 medical conditions were ranked before MCDA was conducted considering, among other things, "medical and societal vulnerability … societal impact … patient perspectives…[and] aspects of solidarity" [563]. Research has been conducted on the criteria that could fruitfully be used as part of MCDA to prioritise innovative medicines in upper middle-income countries [520].

An alternative method is to consider, alongside a technology's ICER, the technology's "*comprehensive benefits and value (CBV) score*" [562]. This is a score that combines how valuable a technology is deemed in terms of "innovativeness, disease severity, and unmet need" [562].

Another method is *DCEA*, which quantitatively breaks down health gains and losses in different populations, e.g., in different socio-economic or demographic groups. This can help decision makers to "make trade-offs between improving total population health and reducing unfair health inequality" [562]. Germany believes that greater weight might be given to distributional aspects in economic evaluation, which actively occurs in Taiwan.

France's HAS considers patient travel time, "using a standardized model to capture those costs" [558]. This may help with geographical equity.

Broader policy approaches extending beyond HTA

Government policy responses can also serve equity-related purposes. For example, the US "introduced a tax credit to incentivize drug development" for orphan drugs and "granted seven-year market exclusivity" to help make medicines for rare diseases profitable [558]. For cancer, there are some dedicated research and medicine funding streams. Such a policy background can at least form a contextual consideration when deciding whether other approaches ought to be used within HTA to give special regard to some disease areas or populations on equity grounds.

In Australia, the life-saving drugs program (LSDP) provides for fully subsidised access to life saving and very expensive medicines for ultra-rare conditions which are rejected for PBS listing on the grounds of cost-effectiveness[144]. The Australian Government has previously indicated that the decision to subsidise access to drugs for ultra-rare conditions at prices that are not regarded as cost-effective is, in part, due to the inherent challenges for sponsors developing medicines for ultra-rare diseases (including high costs of medicines and small treatment populations)[564].

CONSUMER AND STAKEHOLDER EVIDENCE

For the purposes of this paper, consumer and stakeholder evidence is defined broadly, namely as information obtained either directly from consumers or other stakeholders (such as members of the public) or indirectly (e.g., via synthesis of published evidence). The information captures or reflects people's experiences and preferences. It encompasses both patient-based evidence for use in evaluation (e.g., formal patient-preference studies conducted as part of building a primary evidence base) and information on patient's experiences and preferences for use in appraisal (this information might be informal or formalised via a qualitative research study, for instance).

Fifteen jurisdictions, including Australia (MSAC), acknowledged that consumer evidence, especially the patient's experiences, should be an important part of the decision-making process and that this evidence is always considered. Eight jurisdictions solicited the consumer's perspective mainly through written submissions or via questionnaires (Table 59). Input from patients or patient organisations coordinated by a dedicated patient engagement team occurred in three jurisdictions (Canada, CADTH; Wales, AWTTC; Singapore, ACE) and expert opinion suggests at least a further three jurisdictions (France, HAS; UK, NICE; Scotland, SMC). Two jurisdictions (Belgium, KCE; Denmark, DEFACTUM) provided methodology for performing qualitative research to collect patient relevant data and experiences. Expert opinion suggests at least one further jurisdiction (Sweden, SBU).

Expert opinion suggests the following. Most commonly, patient input occurs via written submission and participation in appraisal decision-making meetings. The Patient and Citizen Involvement Group (PCIG) of Health Technology Assessment International (HTAi) provides templates for written submissions. These templates reflect material commonly provided by patients or patient groups, namely information on the impact of the medical condition, its effect on carers, patient experiences with current therapies and the new therapy, and patient expectations. The templates have been used and adapted by EUnetHTA and more recent adopters of HTA, including France, Brazil, Taiwan, and Singapore. While the templates were created for patient organisations, in some jurisdictions they are used by individuals as well. While written submission and meeting participation are the most common methods of involving patients, they are not necessarily well suited to the goals of ensuring that patient involvement occurs dynamically and before, during and after HTA. For this reason, methods that encourage dialogue are a focus of efforts to improve patient involvement. Patients and patient groups may not have sufficient information to write relevant submissions, and without follow-up dialogue written submissions may not sufficiently foster sense-making or capacity building on the part of patients and patient groups. HTAi's PCIG developed 'Values and Standards for Patient Involvement in HTA' using evidence review and an international consensus-building process [565]. This document has guided practice for many HTA bodies, including CADTH, which is reportedly moving away from written

submissions toward dialogue. The 'Values and Standards' document asserts, among other things, the need to appropriately resource and build capacity in patient involvement, and the need for proactive engagement methods, advanced notice for patients prior to involvement opportunities (notably written submissions), and documentation and feedback to patients concerning where patient involvement was most influential and helpful. Facey [286] presents a "mosaic" of patient involvement, whereby the "why" of patient involvement (the goal or value being pursued) informs "who" to involve and "how" (the method best suited) (Table 59).

Table 59 Methods for evaluating non-traditional evidence (consumer evidence)

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Patient submissions /questionnaires			
Expert opinion	Experts panels may consist of medical practitioners, a medical specialty group or consumers. Consumers may provide advice on the relevance of outcomes and on the use of the health technology.	The use of expert opinion should be justified in the introduction of the appropriate section of the report. Use of well-designed methodologies, such as questionnaires and surveys, in the report to reduce uncertainty.	Australia MSAC Guidelines (2021) [290] PBAC Guidelines (2016) [187]
Written submissions from patient and carer organisations	Written submissions from patient and carer organisations can be submitted to NICE to provide perspectives on their experiences. These may be included in the evaluation. Patient experts to be involved throughout the evaluation are chosen based on their experience of the technology and the condition.	NICE selects experts from the nominations received. Patient experts may help clarify issues identified by the technical team (including when scoping), give written evidence, and attend the committee meeting.	UK (NICE) NICE HTA manual (2022) [27]
Patient Group Submissions	SMC accepts submissions from patient groups but not from individuals. SMC provides a summary of the application to patient groups and collects feedback on the draft report. The purpose of the submission is to identify aspects to be included in the HTA report that: May not be captured by the published literature. May not be well captured in QoL or other outcome measures used in clinical trials and other studies. May not be automatically understood by members of SMC.	To take part in the SMC review process, patient groups need to register as a SMC Patient Group Partner. A submission is provided by completing the Patient Group Submission Form. One representative per submitting patient group is able to participate at the SMC committee meeting, to answer questions from committee members, relating to patient and carer issues raised in the submission.	Scotland (HIS) SMC Guide for Patient Group Partners (2022) [318]
EUnetHTA Patient Group Submission Template	Patient organisations can submit patient group input through the online submission template on EUnetHTA's website or via direct contact from assessment teams. This may include one-on-one conversations, groups discussions or scoping e-meetings.	Patient involvement was shown to be most useful in the scoping phase.	Europe (EUnetHTA) Patient Input in REAs (2019) [566]
Questionnaire to affected persons or patient organisations	The involvement of affected persons is usually at the beginning of the HTA project while developing the framework of the topic.	The information can be provided in writing in response to a questionnaire or personally as part of a small focus group. The information provided is considered for relevant outcomes and important subgroups.	Germany (IQWiG) General Methods Version 6.1 (2022) [432]
The National Health Insurance (NHI) patient involvement guideline	The guideline provides the basis for patient involvement in the HTA process in Taiwan. Opinions on new technology related to treating the diseases included in the NHI's major illnesses/injuries list are currently collected for at least 30 days before the application is listed on the agenda for the Pharmaceutical Benefit and Reimbursement Scheme Committee meeting	The online platform enables patients, caregivers, and patient organisations to share information about: the method of information gathering; experiences of living with the conditions/diseases; experiences of the traditional and new treatments; expectations regarding the new treatments; effects on caregivers with/without the new treatments; and other opinions.	Taiwan (CDE) Chen, Huang & Gau. (2022) [132]

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Stakeholder Engagement	The US ICER seeks input from patients and advocacy organisations to provide feedback throughout the HTA process. Stakeholders can provide formal feedback: During an Open Input Period In response to a draft scope In response to a Draft Evidence Report During the public meeting.	Stakeholders may see the results of their feedback during certain milestones in the HTA process, such as recommendations for the population, comparators, and outcomes to be considered.	USA (US ICER) US ICER's Methods Guide (2020) [333]
Key principles of stakeholder engagement	Stakeholder engagement increases the likelihood that the important and relevant issues are identified and prioritised. The extent to which stakeholders are involved varies for each HTA and could include: Information gathering –about attitudes, opinions and preferences. Consultation –feedback on specific findings. Participation –actively involved at all stages.	Successful implementation of stakeholder engagement requires: Inclusiveness, Transparency, Commitment, Accessibility, Accountability, Responsiveness and Willingness to learn.	Ireland (HIQA) Guidelines for Stakeholder Engagement (2014) [140]
Input from patients or patient organisations coordinated by a dedicated patient engagement team			
CADTH Framework for Patient Engagement	To improve the quality of HTA assessments of drugs. CADTH has a dedicated patient engagement team. CADTH uses email, Twitter, and Facebook to call for patient input and stakeholder feedback.	Patient input is used to inform and design assessment protocols; to interpret trial results; to identify use, equity, and ethical considerations.	Canada (CADTH) CADTH Framework for Patient Engagement (2022) [275]
The Patient Access to Medicines Service (PAMS)	PAMS identifies relevant patient organisations. The submission form also asks pharmaceutical companies to list relevant patient organisations. Patients/carers/patient organisations are invited to describe their experience	The appraisal committees are informed of the patient perspective from the responses.	Wales (AWTTC) Pathways for access to medicines (2017) [240]
CEE team	All patient involvement in ACE's technical evaluations is coordinated by the CEE team. CEE staff draft and distribute surveys and collate responses from the relevant patients and patient organisations.	The experiences of patients and carers provide important evidence to help inform advisory committees about: how the medical condition affect patients and carers unmet needs, preferences, and expectations of patients benefits and disadvantages of the health technology identify health outcomes that are important to patients determine if the outcomes measured in clinical trials and economic models are relevant to the Singapore context address uncertainties in the evidence potential issues around the use and access of the health technology	Singapore (ACE) Process and methods guide for patient involvement (2023) [440]

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Formal methods for obtaining the patients perspective using qualitative research (patient interviews, focus groups etc)			
Qualitative Data	The KCE Process Book provides details on carrying out qualitative research to collect patient relevant data. Methods include: Semi-structured individual interview Focus groups Observation The Delphi survey	One of the strengths of qualitative research is that it studies people in a clinical setting rather than in an experimental one.	Belgium (KCE) KCE Process Book (2021) [435]
Measurement of patient-experienced quality	The HTA Handbook includes methods for generating, analysing and reporting qualitative and quantitative research to collect patient relevant data. Qualitative methods include: individual interviews focus group discussions and interviews participant observation fieldwork. Quantitative methods include: questionnaires surveys.	Primary quantitative research is only considered relevant if the evidence retrieved from a literature review proves inadequate	Denmark (DEFACTUM) HTA Handbook (2007) [139]

ACE = Agency for care effectiveness; AWTTC = All Wales Therapeutics & Toxicology Centre; CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation; CEE = Consumer Engagement and Education; DEFACTUM = Social & Health Services and Labour Market; EUnetHTA = European network for Health Technology Assessment; HIQA = Health Information and Quality Authority; HIS = Healthcare Improvement Scotland; IQWiG =Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; KCE = The Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PAMS = Patient Access to Medicines Service; QoL = Quality of life; REAs = Relative Effectiveness Assessments; SMC = Scottish Medicines Consortium; UK = United Kingdom; USA = United States of America; US ICER = US Institute for Clinical and Economic Review.

Table 60 Proposed Methods of Patient Engagement in HTA

When (stage)	Why (goals/values)	Who (to involve)	How (proposed methods or mechanisms)
Public sector funding decision for research to address uncertainties (before or after HTA)	Relevance	Patient groups Individual patients	Participation in decision-making committee or other forms of priority setting process for defining research priorities for public funding
Development of HTA processes	Relevance	Individual patients Patient groups	Consultation/research on assessment methods
	Fairness Legitimacy	Patient groups	Workshops and use of feedback from patient groups to develop patient participation methods
	Relevance Fairness Legitimacy	Patient groups	Formally evaluate and research patient participation methods

When (stage)	Why (goals/values)	Who (to involve)	How (proposed methods or mechanisms)
	Fairness	Patient groups	Publish a policy for patient participation that indicates patients' rights and process for participation
Proposal of HTA topics	Relevance	Patient groups	Submission of potential topics online or via paper form (with support from HTA researchers to complete the form)
	Relevance	Individual patients (incl. informal caregivers / carers	Group discussion (focus group, Delphi, etc.) with HTA researchers to identify potential topics
	Fairness	Patient groups	Public consultation on proposed topics and policy questions
	Relevance	Patient group member	Patient representative on selection committee for a themed call of topics
Communication	Fairness	Patient groups	Notification of timelines for an HTA including points at which patient groups can participate
	Fairness	Patient groups	Accessible reports and communication methods that take account of the limitations of the condition and possible comorbidities
	Legitimacy	Individual patients	Media campaigns to communicate the HTA recommendations
Building capacity for patients to contribute	Building capacity Fairness	Patient groups	Dedicate HTA staff to work on patient involvement and provide patient groups with a named individual to contact
	Building capacity	Patient groups	Feedback in person or writing on submission to HTA committee
	Building capacity	Individual patients	Deliver training courses led by HTA staff
		Patient groups	
	Building capacity	Patient groups	Contribute to training courses developed by patient groups
	Building capacity	Patient groups	Support network meetings of patient representatives who are participating in HTA or may do so in future
	Building capacity	Patient groups	Promote trusted online training resources
	Building capacity	Patient group members	Support attendance at HTA conferences with travel grant
	Building capacity	Individual patients	Payment for travel, loss of earnings, preparation of submission
		Patient groups	
	Building capacity	Patient groups	Organize a buddying system among patient representatives
	Legitimacy	Patient groups	Include patient representatives in conference organization committees
	Fairness Relevance	Patient groups	Offer grants for projects related to HTA
Scientific advice on study design	Relevance	Individual patients	Patients considered equal expert in scientific advice meeting
	Relevance	Individual patients	Meeting led by HTA researcher to elicit issues to feed into scientific advice meeting
HTA scoping/protocol development	Relevance	Individual patients	Interviews/focus groups to identify key issues to hone research questions and identify priority patient populations (e.g. with high unmet need)
	Relevance	Patient groups	Stakeholder consultation on draft scope/protocol and PICO framework

When (stage)	Why (goals/values)	Who (to involve)	How (proposed methods or mechanisms)
	Relevance Equity Fairness	Individual patients	Workshop to discuss PICO framework
Primary or secondary research	Fairness Equity	Patient groups	Input to design, conduct, and reporting of research as per public research guidance
Submission of patient input	Fairness Relevance	Patient groups	Via clear template with supporting guidance and assistance from HTA staff
		Individual patients	
Consultation on draft report	Relevance	Patient groups	Stakeholder review of draft reports to ensure all relevant patient issues have been included
	Equity	Patient groups	Comment on clarity of draft recommendations
	Fairness	Disadvantaged patients	Meetings to discuss draft findings
Multi-stakeholder review/appraisal of evidence/development of recommendations	Fairness Equity Legitimacy	Individual patients	Expert testimony to appraisal committee
	Fairness Equity Legitimacy	Patient groups	Comments on issues that might have been misunderstood and discusses value of treatment to patients
	Relevance Legitimacy	Patient groups	Separate section of HTA report summarises patient aspects
	Legitimacy Relevance	Patient groups	Summaries of patient input
		Public representative	
Appeal	Fairness Legitimacy	Patient groups	As a stakeholder according to defined appeal process, or to the courts
Communication	Relevance	Patient groups	Input to development of patient-friendly summaries of HTA
	Legitimacy	Patient groups	Participation in press conference about HTA decision
		Individual patients	
	Legitimacy	Patient groups	Dissemination of HTA recommendation
	Relevance	Patient groups	Share patient group submission with umbrella patient organisations
Managed entry to health service	Equity Legitimacy	Patient groups	Act as ‘safe harbour’ to provide governance on data collection systems for managed entry agreements

Adapted from Facey 2017 [286]

Deliberative approaches

As with equity, group deliberation is regarded as a central method for integrating into appraisal decision-making considerations that arise from stakeholder engagement. Research has described "evidence-informed deliberative processes", which allow included stakeholders to learn from one another and to engage in a structured discussion based on important considerations, or "identified decision criteria" [567]. However, research suggests that "there is little documentation and research to inform the development of effective and efficient deliberative processes, and to evaluate their quality" [568]. With that said, guidance for good deliberative procedures in HTA has been produced [569]. And some markers of quality deliberation have been proposed by researchers (Table 61).

Table 61 Core Principles and Actions for Deliberative Processes in HTA

Principle	Potential Supporting Actions
Transparency Deliberative processes and the basis for a recommendation and/or decision should be explicitly described and made publicly available. The more broadly this description is made available (for example, not only to those participating in the process) the more support this principle has. The transparency of a deliberative process should be both forward- and backward-looking.	Prior to a deliberation, there should be sufficient information and guidance available about the deliberative process to allow any interested person to understand: The nature of the decision that needs to be made Who will be involved in making the decision as (a) a member of the deliberative body, or (b) as a participant in the process How the final decision will be made, for example, by consensus or majority vote The factors or aspects of value that will be deliberated upon (and perhaps what is not considered) and the types of information that might influence the decision and how that information will be gathered Following a deliberation, information and guidance should be sufficient to allow any interested person to understand: What the decision was and what options or alternatives were considered What the facts and reasons were for the decision (to the greatest extent possible) Who was involved in making the decision as (a) a member of the deliberative body, and (b) as a participant in the process Communication materials are developed to ensure that this understanding is possible for the broadest range of people, that is, people with different levels of education, technical training, etc.
Inclusivity HTA deliberations are best informed when all involved work together. The right perspectives should be included so that decision making has the best chance of reflecting the reality of people impacted and, as much as possible, living up to their values.	Committees are composed of a sufficient number of people so that, together, they have the relevant knowledge, skills, and character required to do this work well, and ensure appropriate representation The process for identifying and selecting committee members is clearly described Stakeholders are supported to make deliberations as robust and as informed as possible (for example, sharing data, materials in lay language, education). Meaningful opportunities for all stakeholders to be involved are described The views and perspectives of stakeholders are genuinely considered and responded to The deliberative environment and dialogue are organized and facilitated to minimize power differences among participants All interactions and activities are respectful of the dignity, worth, rights, beliefs, values, preferences, customs and cultural heritage of all involved Deliberations are made public to the greatest extent possible, and, if some or all aspects are not in public, the reason for this is described and justified

Impartiality The deliberative process used for each decision, and those involved in it, should be perceived to be free from undue influences, both internal (for example, from the agency supporting the HTA process) and external (vested interests in a given topic), and independent.	All people involved in the deliberative process understand their roles and responsibilities A clear description of how direct and indirect conflicts of interests of those involved in deliberation are identified and managed, including definitions of quantitative thresholds for certain types of conflict and management actions (for example, no voting) All participating stakeholders declare their conflicts of interest using an agreed and standard format The chair or facilitator of the deliberation manages the discussion to achieve equitable input and prevent the undue influence of their own opinions in moving the group toward a maximally informed decision

Source: Bond, Stiffell and Ollendorf (2020) [568]

Researchers have studied how information from patient engagement is handled and weighed in committee deliberation as part of NICE's STAs [570]. The researchers found "disagreement among the committee when weighing-up patient statements" [570]. Patient experts reported feeling intimidated and unsure of their role in NICE meetings, where "the emphasis on clinical and cost-effectiveness overshadowed patient issues" [570]. The patient experts' inclusion thus felt "tokenistic" [570]. Researchers found that the Chair was critical in opening a dialogical space, and fostering a broader institutional culture, in which "experiential evidence, interpretations and opinions" could be taken seriously alongside "rigorous evaluations and scientific rationality" [570]. This finding connects to Paper 1 of the HTA Review ('International health technology market approval, funding and assessment pathways'), which noted that researchers have recommended explicitly acknowledging different epistemic traditions to help those traditions meaningfully combine in the service of decision making. In NICE, the prioritisation of one evidence type over another created tensions between committee members, as did "suspicion towards the patient group, who were regarded as colluding with the drug manufacturing industry". For evidence of such suspicion in Australia, see Lopes et al 2015[128]in which a past or current chair of one of Australia's Advisory Committees commented as follows:

"The perception of conflict of interest has always been present and has always potentially, in some people's eyes, reduced the veracity of the information from consumer groups that are funded by drug companies. Now, I personally don't have any issues with that, I understand that it's a perceived conflict of interest".

Expert opinion suggests that such concerns demonstrate a need to train committee members, given that measures are used to capture conflicts of interest and to collect valid patient perspectives. The tensions in NICE functioned to increase decision-making complexity. The committee found the patient experts' "impassioned accounts too emotional or hard to handle", yet the patient experts were precisely "expected to present themselves as a credible patient while at the same time performing the role of a charismatic patient representative" [570]. The researchers concluded that "NICE needs to provide much greater guidance and clarity over the roles and contributions it expects patients to make and how their statements and submissions might fit into the decision-making framework" [570].

Other researchers claim that "patient insights can help committee members interpret HTA evidence", even while there is "great variation in how committee members

approach "experiential evidence"" [276]. While this variation exists in Scotland, patient statements nonetheless "provide context, making HR-QoL scores collected in clinical studies more meaningful" for decision makers [276].

Belgium and New Zealand used public engagement to "define new reimbursement criteria", which placed greater emphasis on patients', families' and caregivers' QoL [563]. Both countries recognised that patient and societal perspectives had to be considered, "but separately and explicitly", and with an acknowledgement of diverse perspectives instead of a single public preference [563]. Both countries recognised the importance of an explicit list of considerations to inform what was ultimately human judgement sensitive to context, as opposed to "weighted criteria with some sort of formulaic approach to decision making" (like MCDA), which the public did not favour [563]. Researchers have also examined patient involvement at the organisation level, as distinct from at the level of individual HTAs[571]. As per the level of individual HTAs, patient involvement occurred to serve both "the democratic goal of "legitimacy"" and the instrumental goal of enhancing the information used in individual HTAs, though HTA bodies favoured the latter goal more than patient and citizen participants (PCPs). The HTA bodies and PCPs also differed on how to evolve patient engagement. For instance, HTA bodies sought to increase patients' "operational involvement" in HTAs, while PCPs wanted more training and experience, closer proximity to HTA body decision makers, an expanded role in HTA (including in horizon scanning), and for HTA bodies to speak more directly to the public[571].

Expert opinion suggests that, for HTAi's PCIG, the main ethical considerations relating to patient involvement concern, not conflicts of interest, but the burden of involvement on patients, a lack of transparency concerning information, and whether the patient inputs are responsibly used. Some researchers also regard as important ethical considerations appropriately balancing risks and benefits for all HTA participants, "selecting and engaging patient participants in an ethical way", and "decreasing the influence of power and information differentials between patients and other HTA members"[572].

Expert opinion suggests that some thinking in HTA has evolved from focussing on patient input to patient partnership and co-design, and that HTAi's PCIG has developed an unpublished framework for evaluation, whereby the impact of patient involvement might be reported (in funding recommendations, for instance).

Quantitative approaches

The use of factors important to patients (like career goals) "merely" as contextual inputs to deliberation has been criticised as inadequate, with a call for greater integration of them into economic modelling and making methodological advances to achieve this [573].

A systematic review identified 61 value frameworks and MCDAs that considered patient experiences, though often "superficially, without clear definitions" [519]. Researchers

built on these to propose five domains of patient experience: a health technology could be assessed in terms of (1) its responsiveness to patients' individualised needs; (2) how it stands to improve health literacy and empower patients; (3) how it improves outcomes that patients and caregivers report as being important; (4) its financial impact on households; and (5) how it stands to improve access to care for vulnerable patients [519]. The researchers suggest that these five domains could be used to inform MCDAs, to augment cost-effectiveness analysis (namely as equity weights) and at least to help standardise deliberative decision-making at the HTA appraisal stage.

NICE welcomes industry providing *patient preference studies* as part of its evidence submissions, but it does not want "patient preference data to be directly incorporated into health economic modelling" [574]. This may be so NICE can compare value for money across conditions or disease areas. Like NICE, HTA agencies in Canada, Belgium and Germany have expressed interest in using patient preferences "for scientific advice and value assessments, but not through incorporation" into QALYs and MCDA, because there is already a lot packed into the QALY and MCDA can be too rigid and misused [575]. The agency representatives differed greatly in how much weight they thought patient preferences ought to be given (from almost none to more than any other stakeholder's preferences). They were unsure about how much impact a patient preference study would have in appraisal decision making, but if the study was good enough they thought it could have some impact, such as increasing decision maker confidence in their decision [575, 576].

Patient preferences have been elicited to replace or supplement use of the QALY in Germany and Sweden, respectively [575, 577]. Researchers propose that patient preference studies could be used in HTA for "understanding what matters to patients, predicting patient choices, estimating the utility generated by treatment benefits, estimating the willingness to pay for treatment benefits, and informing distributional considerations", though the latter is "not recommended" [578]. (This is potentially in line with NICE's practice and because other factors like cost matter [575].) Researchers argue that methodological challenges are preventing patient preference studies from being more included in HTA appraisal decision making [579]. Greater clarity is needed (e.g., from decision making bodies) on how patient preference studies ought to be conducted but also on how they would be used in regulatory and HTA decision making [578, 579]. There is ongoing debate on how patient preference data ought to relate to QALY calculations, which otherwise use public (non-patient) preferences [579].

Public preferences are widely used, mostly "collected using time-trade off or standard gamble methods to inform health state utility estimation" [577]. Public preferences have also been elicited using "choice-based methods" to identify outcomes of importance beyond the QALY in England, Wales, The Netherlands, and Scotland [577]. Public preferences have been used to formalise "preferences for nonhealth factors" in reimbursement and pricing decision making, "using either rating or pairwise methods with decision makers (Austria, Hungary, Italy), choice-based methods with citizens (Belgium), or matching methods with caregivers (France)" [577]. The Netherlands and

Sweden have used public preferences to estimate a willingness-to-pay for the QALY (i.e., an ICER threshold) [577].

METHODS FOR SPECIFIC POPULATIONS AND TECHNOLOGIES

The literature on methods for special populations was sometimes difficult to distinguish from the literature for special technologies. Results from the literature search have been categorised into broad themes, in which there may be some overlap between methods to address population related issues (such as rare diseases) or to address technology related issues (cell and gene therapies), and judgement has been used to assign articles to categories (Table 62).

The scoping search identified eleven articles describing methods or the use of methods by HTA agencies when considering treatments for special populations. Most of the articles addressed methods for assessing orphan drugs or HTA involving rare diseases. Three articles were identified that reported on non-rare diseases: and one discussed value frameworks for assessing treatments for paediatric populations.

Table 62 Studies of methods relevant to special populations

Category	Included citations	Description of evidence
Orphan drugs	Baran-Kooiker, Czech and Kooiker (2018) [580]	MCDA models for HTA of orphan drugs
	Blonda et al (2021) [550]	European Value Assessment Frameworks for orphan drugs
	Mohammadshahi et al (2022) [581]	Scoping review of methods for the assessment of orphan drugs
	Charlton (2022) [582]	Eliciting NICE's considerations for priority setting for highly-specialised therapies (for rare diseases).
Rare diseases	Nestler-Parr et al (2018) [583]	Challenges in HTA of rare disease technologies
	Ollendorf, Chapman and Pearson (2018) [584]	Valuing treatments for rare diseases
	Nicod et al (2023) [585]	Improving QoL assessments for rare diseases
	Cho et al (2022) [586]	Applicability of evidence for targeted therapies from common cancers to rare cancers
	Wagner et al (2023) [587]	HTA challenges for rare disease interventions by different value dimensions
	Whittal, Meregaglia and Nicod (2021) [588]	Challenges of patient reported outcomes in rare diseases
Paediatric HTA framework	Gauvreau et al (2023) [589]	Citizen identified components of a paediatric HTA framework

HTA = Health technology assessment; MCDA = Multiple criteria decision analysis; NICE = National Institute for Health and Care Excellence; QoL = Quality of life.

The scoping review identified 25 articles describing methods for specific technologies. More than half of these articles addressed methods for ATMPs. Articles discussing artificial intelligence, vaccines, histology independent therapies, antimicrobials,

genetic / genomic guided therapy, immunotherapy, complex technologies and high-cost treatments were also identified Table 63.

Table 63 Studies of methods relevant to special technologies

Category	Included citations	Description of evidence
Advanced Therapy Medicinal Products (ATMPs): Gene replacement therapies and/or Cell therapies	Aballéa et al (2020) [590]	Methodological issues for the evaluation of gene replacement therapies
	Angelis, Naci and Hackshaw (2020) [591]	Methodological refinements for assessments of cell and gene therapies.
	Coyle et al (2020) [517]	Methods and value frameworks for evaluation and decision making for cell and gene therapies
	Gozzo et al (2021) [592]	Comparison of HTA for ATMPs across 3 European Countries
	Jönsson et al (2019) [536]	HTA assessment principles and practices for ATMPs
	Landfeldt (2022) [537]	HTA Challenges for gene therapy of neuromuscular diseases.
	O'Hara and Neumann (2022) [593]	Value assessment of gene therapies used to treat haemophilia.
	O'Mahony et al (2022) [541]	Value assessment and HTA methods for gene therapies used to treat haemophilia.
	Pani and Becker (2021) [538]	HTA processes and methods for evaluating specialised therapeutics (ATMPs)
	Pinho-Gomes and Cairns (2022) [90]	Review of the evaluations of ATMPs by NICE
	Qiu et al (2022) [594]	Systematic review of the challenges for regenerative medicines (ATMPs) to receive market access.
	Qiu et al (2022) [595]	Considerations in evidence generation for gene therapy to facilitate fit-for-purpose HTA
	ten Ham et al (2022) [542]	Considerations in the HTA of ATMPs in Scotland, The Netherlands and England
Artificial intelligence (AI)	Bélisle-Pipon et al (2021) [596]	Description of HTA concerns for health technologies containing or created by AI.
Vaccines	Bell, Neri and Steuten (2022) [413]	Broader value framework for vaccines.
	Brassel et al (2021) [213]	Broader value framework for vaccines
High-cost treatments	DiStefano et al (2021) [597]	Use of Added Therapeutic Benefit to assess ultra-expensive drugs.
Tumour Agnostic / Histology-Independent	Gaultney et al (2021) [598]	Framework for the assessment of histology-independent cancer therapies
	Lengliné et al (2021) [599]	Methods for assessing basket trials by HTA in France.
	Schiller et al (2023) [600]	Challenges and solutions for the benefit assessment of tumour agnostic therapies
Antimicrobials	Hillock et al (2020) [601]	Value assessment of antimicrobials in Australia and implications for development, access and funding.
	Morton et al (2019) [367]	Value attributes of novel antibiotics for consideration in HTA decision making.
	Schurer et al (2023) [335]	Description of NICE's subscription-style payment model for antimicrobials
	Gotham et al (2021) [177]	Reimbursement models for antimicrobials across France, Germany, Sweden, UK and the USA.
Complex technologies	Hogervorst et al (2022) [602]	Survey of European HTA agencies to identify key challenges in HTA of complex health technologies.
Immunotherapy	Quinn et al (2022) [603]	Key issues relating to estimating the long-term benefits of immunotherapies.

Precision medicine / genomic profiling	Love-Koh et al (2018) [604]	Identification of precision medicine developments and implications for HTA.
	Tarride, Gould and Thomas (2022) [605]	Limitations of HTA processes for considering comprehensive genomic profiling.

AI = Artificial intelligence; ATMPs = Advanced Therapy Medicinal Products; HTA = Health technology assessment; NICE = National Institute for Health and Care Excellence; UK = United Kingdom; United States of America.

ORPHAN DRUGS AND RARE DISEASES AND UNMET NEED

HTA Agency websites from the included jurisdictions were searched to identify specific methods for evaluating the following populations:

- Rare diseases or small populations (limited data)
- Populations with unmet clinical need
- Equity considerations for vulnerable and disadvantaged populations

The specific methods that were identified are summarised below.

Rare diseases

Rare diseases are generally defined as life-threatening or chronically debilitating conditions with a low prevalence rate. There is no over-arching consensus for the minimum prevalence rate required to define a rare disease, and consequently it varies from country to country. Below is a list of countries and the prevalence rate used to define a rare disease. According to the Australian Government Department of Health and Aged Care, a disease is considered rare if it affects fewer than 5 people in 10,000. An additional Australian estimate provided in the list below represents the prevalence eligibility criteria for a drug to be considered by the life-saving drugs program.

USA	≤668 per 100,000
Japan	≤407 per 100,000
World Health Organisation	≤65 out of every 100,000
EU	≤50 out of 100,000
UK/Scotland	≤50 out of 100,000
Australia	≤50 out of 100,000
Canada	<50 in 100,000
Singapore	<40 in 100,000 people (<1600 people)
Sweden	≤10 per 100,000
Australia-eligibility for LSDP	≤2 per 100,000 (around 500 people)
Norway	≤1 per 100,000 globally (≤50 people)

It is important to note that the definition of a rare disease and an orphan drug may vary across jurisdictions. However, in most cases, concerns relating to the generation of evidence or the application of HTA for technologies for rare diseases will be similar regardless of the definition.

Sixteen jurisdictions, including Australia (PBAC), considered that orphan drugs for rare or very rare diseases should have a specialised evaluation pathway, only ten jurisdictions provided any guidance for undertaking the associated HTA evaluation report. One jurisdiction reported that no special pathways were used to evaluate orphan drugs. Three jurisdictions did not provide any documentation on their website to indicate if specialised evaluation pathways were available or not.

Generally, the orphan drug is evaluated in the same way non-orphan drugs are, but special consideration is given according to the specific guidelines for each jurisdiction, often with continued assessment of the clinical effectiveness during the early access period.

Unmet clinical need

Six jurisdictions indicated that medicinal products for populations with an unmet clinical need were given additional consideration during the decision-making process. Australia (PBAC) provided guidance on how to incorporate information pertaining to the severity of the unmet need into the evaluation. Both Australia and France consider the unmet need when assessing the clinical effectiveness of the medical product. England and France both had Early Access to Medicines Schemes for medicinal products with the potential to be of value in areas of unmet medical need (Table 64). No details were provided by the other three jurisdictions.

Table 64 Methods for special populations and technologies identified in HTA agency reports

Method	Purpose	Requirements/Assumptions/Limitations	Reference
Orphan drugs for rare or ultra-rare diseases			
Life-Saving Drugs Program (LSDP)	The LSDP enables patients with rare and life-threatening diseases to access essential and very expensive medicines.	The drug must have been considered by the PBAC and found to be clinically effective but not cost effectiveness, and consequently rejected for PBS listing.	Australia (PBAC) Life Saving Drugs Program (2018)[144]
The evaluation of highly specialised technologies (HST)	HSTs are selected using the following criteria, all of which have to apply: The target patient group is small and distinct, and treatment will occur in a few centres. The condition is chronic and severely disabling. The technology is expected to: be exclusively used in the context of a highly specialised service. be likely to have a very high acquisition cost. has the potential for life long use The need for national commissioning is significant.	Evaluation is based on NICE's Guide to the Process and Methods of Technology Appraisal. Variations in the evidence base due to the limitations associated with very rare conditions are permitted.	UK (NICE) Methods of the Highly Specialised Technologies Programme (2017) [606]
The New Pathway for Ultra-Orphan Medicines	The new pathway consists of four key steps: 1. Validation as an ultra-orphan medicine by the Scottish Medicines Consortium (SMC) 2. An initial full clinical and cost effectiveness assessment by the SMC 3. The pharmaceutical company must collect data to generate evidence for up to three years 4. A full update of the submission must be lodged following the three-year data collection period.	To enable an ultra-orphan medicine to be available through this pathway, the pharmaceutical company must comply with the standard terms and conditions considered acceptable by the Patient Access Scheme Assessment Group and support the data collection via a Patient Access Scheme that meets requirements for assessment under the ultra-orphan pathway.	Scotland (HIS) Guidance for Ultra-Orphan Medicines (2018) [425]
Regulation (EC) No 141/2000	The guidelines indicate that orphan medicinal products are regulated by the European Parliament and of the Council of the EU according to Regulation (EC) No 141/2000 of 16 December 1999.	Regulation (EC) No 141/2000 states that to obtain the designation of an orphan medicinal product, an application to the European Agency for the Evaluation of Medicinal Products must be submitted at any stage of the development of the medicinal product before the application for marketing authorisation is made.	Europe (EUnetHTA) HTA Core model Version 3.0 (2016) [136]
Early access to medicinal products	A scheme enabling the early availability and reimbursement of a medicinal product indicated for a severe, rare, or debilitating disease, when the following conditions are met: There is no appropriate treatment, and it cannot be deferred. The efficacy and safety of the medicinal product are strongly presumed based on trial results. This medicinal product is presumed to be innovative.	The HAS assessment is based on all the clinical data available at a given time. Early access authorisations are subject to complying with a protocol for temporary use and data collection set out by the HAS.	France (HAS) Early access to medicinal products guide (2021) [54]

Method	Purpose	Requirements/Assumptions/Limitations	Reference
		It allows the collection of observational or RWD from patients receiving an early access medicinal product under routine care conditions.	
Conditional Reimbursement	To enable reimbursement of health care that does not fulfil the statutory criterion for effectiveness.	During a maximum of four years from conditional entry, data must be collected on effectiveness, and/or cost-effectiveness.	Netherlands (ZIN) Conditional reimbursement of health care (2012) [447]
The Rare Disease and Orphan Drug Act	After receiving the designation of orphan drug, listing in the NHI Pharmaceutical Benefits and Reimbursement Scheme can be apply for.	Fewer rare diseases are recognized in Taiwan due to differences in the definitions applied compared with the EU and the USA. For example, cancers are not recognized as rare diseases in Taiwan while they could be categorized as rare diseases in both the EU and the USA.	Taiwan (CDE) Hsiang et al (2021) [51]
Orphan Drug Reimbursement in Belgium	Submissions for orphan drugs follow the same procedure as for Class I pharmaceutical products that claim a therapeutic added value.	However, no pharmacoeconomic evaluation must be submitted for orphan drugs	Belgium (KCE) Policies for Rare Diseases and Orphan Drugs (2009) [88]
Arrangements for assessment of pharmaceuticals for very small patient groups with extremely severe conditions	To provide guidance on submitting documentation for single technology assessment of pharmaceuticals indicated for very small patient groups with severe conditions	Less stringent requirement for documentation of the benefit of the interventions can be accepted. However, this will result in greater focus on monitoring to document the benefit of the treatment in clinical practice.	Norway (NIPH) Assessment of pharmaceuticals for very small patient groups (2017) [164]
The Rare Disease Fund (RDF)	All public healthcare institutions can propose new medicines for inclusion in the RDF each year and each potential topic is prioritised for evaluation by ACE	The ACE technical team prepares a clinical briefing document, which includes a summary of published clinical evidence, funding decisions from overseas reference agencies, local costing information and published prices in five overseas reference jurisdictions (Australia, New Zealand, UK, South Korea, and Taiwan), when available.	Singapore (ACE) Drug and Vaccine Evaluation Methods (2021) [439]
Populations with unmet clinical need			
Determining clinical need	Less-readily quantifiable factors that influence PBAC decision making include the clinical need for the proposed medicine.	The availability of effective therapeutic alternatives is used to determine the extent of the clinical need. Expert opinion can be useful in determining the clinical need	Australia (PBAC) PBAC Guidelines (2016) [187]
Promising Innovative Medicines (PIM) designation	A PIM designation indicates that the medicine may be a candidate for the Early Access to Medicines Scheme, based on the evidence to date. It also may be of value in areas of unmet medical need.	The topic progresses through the usual NICE Topic Selection process, except that products with a PIM designation are prioritised.	UK (NICE) Early Access to Medicines Scheme (2016) [441]
Unmet medical need in HTA assessments	Addressing an unmet medical need is considered in the assessment as: An element for assessment of the clinical benefit and access to reimbursement	The following criteria are considered when taking medical need into account:	France (HAS) Assessments and appraisal for

Method	Purpose	Requirements/Assumptions/Limitations	Reference
	A criterion informing the clinical added value An element in favour of an accelerated assessment procedure.	The quality of the clinical trial, which includes the choice of comparator(s), the methodological quality of the study, the appropriateness of the population included, the relevance and significance of the clinical endpoint, etc. The effect size in terms of clinical efficacy, QoL and safety The clinical relevance compared to clinically relevant comparators	reimbursement purposes (2020) [430]
Early access to medicinal products	A scheme enabling the early availability and reimbursement of a medicinal product indicated for a severe, rare, or debilitating disease, when the following conditions are met: There is no appropriate treatment, and it cannot be deferred. The efficacy and safety of the medicinal product are strongly presumed based on trial results. This medicinal product is presumed to be innovative.	The HAS assessment is based on all the clinical data available at a given time. Early access authorisations are subject to complying with a protocol for temporary use and data collection set out by the HAS. It allows the collection of observational or RWD from patients receiving an early access medicinal product under routine care conditions.	France (HAS) Assessments and appraisal for reimbursement purposes (2020) [430]

ACE = Agency for Care Effectiveness; EU = European Union; EUnetHTA = European network for Health Technology Assessment; HAS = Haute Autorité de Santé; HIS = Healthcare Improvement Scotland; HST = Highly specialised technology; HTA = Health technology assessment; KCE = Belgian Health Care Knowledge Centre; LSDP = Life Saving Drugs Program; NHI = National Health Insurance; NICE = National Institute for Health and Care Excellence; NIPH = Norwegian Institute of Public Health; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PIM = Promising Innovative Medicines; QoL = Quality of life; RDF = Rare Disease Fund; RWD = Real-world data; SMC = Scottish Medical council; USA = United States of America; ZIN = Zorginstituut Nederland.

The literature highlighted current challenges of evaluating technologies for rare diseases faced by HTA agencies. These include:

1. **Lack of sufficient and robust clinical data** [90, 583, 587]

   Wagner et al (2023) reported on a review of 125 EMA authorisations for orphan drugs between 1999 and 2014, and found that most drugs did not have at least 2 trials, and a third of all trials did not contain a control arm and a third were not randomised [587]. The literature often cites challenges in randomisation of patients with rare diseases, particularly if the disease is severe with few alternatives [538]. Pinho-Gomes and Cairns (2022) reported on NICE assessments of 14 ATMPs (often for rare diseases), and found that most assessments included single arm studies, and some employed unanchored comparisons to historical cohorts [90].

2. **Insufficient knowledge of the natural history of the disease** [583, 587, 593] **and no established standard of care** [583, 594].

   Given that many orphan drugs and technologies for rare diseases are not accompanied by controlled studies, the lack of understanding of the natural history of the disease undermines the ability to confidently generate effectiveness estimates. The lack of robust data informing natural history also presents a challenge for establishing links between intermediate and final outcomes. This is especially important when clinical studies are short, yet the disease studied is slowly progressing, such that an estimate of the duration of effect and impacts of the technology on the trajectory of the disease are critical to estimating value.

3. **Lack of methods to assess effectiveness** [583]

   Methods for the evaluation of indirect comparisons are commonplace, however, there are no well accepted methods available to estimate a treatment effect where no comparator group is available. Furthermore, complex methods to generate RWE are difficult to validate, and do not necessarily increase certainty in the estimate of effectiveness. O'Hara and Neumann (2022) suggest that many studies of treatments for haemophilia use intra-patient comparisons (before / after comparisons), which permits an assessment of short term changes in treatment utilisation and HR-QoL, but does not permit the observation of impacts on long term outcomes [593].

4. **Justification for ICER thresholds** [582, 584, 587]

   Establishing whether a treatment for a rare disease represents an efficient use of resources is challenging. Notwithstanding the limitations associated with establishing a robust estimate of a treatment effect, orphan treatments are often accompanied by high prices. Providing a rationale for recommending an orphan treatment with a substantially higher ICER than a more common drug may present a challenge to decision-makers.

5. **Insufficient understanding of the relevance of the reported treatment effects from both a clinical and patient perspective** [587]

   As surrogate outcomes are often all that is available to HTA agencies when assessing drugs for rare diseases, there can be a disconnect between the relevance of outcomes to clinicians and the priorities of patients. A lack of valid patient reported outcome measures in rare diseases has been commonly identified [585, 588].

6. **Challenges relating to other HTA domains** [587]

   The assessment of technologies for rare diseases may have greater challenges outside the usual clinical and economic domains than for more common treatments. The organisational impact associated with the provision of technologies for rare diseases may be great if the technologies require specialist training and monitoring[587]. There may be additional social and ethical tensions that are relevant to the assessment of treatments for rare diseases. The paucity of data on many rare diseases raises uncertainties regarding the likely social and organisational impact of reimbursing an orphan treatment.

7. **Proposed methodological solutions for identified challenges**

   It is important to highlight that most solutions proposed by the included articles include methods to improve the quality of the data collected rather than methods for assessing poor quality data. Many studies discussing limitations of evidence for treatments for rare diseases recommend ongoing data collection, and several state that this ideally should occur with cross-country collaboration.

Despite identifying a range of challenges, few definitive methods or solutions to the challenges were proposed. Wagner et al (2023) recommended, in response to clinical challenges, rigorous analysis of the quality of the clinical data and an in-depth assessment of the methods used to generate evidence [587]. They augment this approach with consultations with clinical experts and patients. However, this recommendation does not solve for the key issue, which is a lack of high quality, trustworthy, applicable, comparative data. While clinician and patient input can assist HTA understand the context and impact of the disease, it is unlikely to assist in the estimate of the magnitude of the effect of the orphan treatment.

In response to the problems inherent with the use of generic PROMs for patients with rare diseases, Whittal, Meregaglia and Nicod (2021) proposed a range of solutions for researchers that included optimising methods for PROM development [588]. Such solutions do not typically fall within the remit of an HTA agency. Nicod et al (2023) reported proposed solutions derived from a mixed methods approach [585]. They proposed that HTA must: understand the QoL impacts of the disease and treatment; critically assess the patient reported outcome data, considering what matters most to the patient population; accept that a lack of significant effect does not imply no QoL benefit; use patient input to understand QoL impacts; and, provide guidance to capture

QoL impacts on patients and carers. The key message from Nicod et al (2023) is that, for rare diseases that are poorly understood, HTA must seek additional evidence from patients, patient groups or their carers [585].

A key tool for mitigating the risk associated with the reimbursement of high-cost technologies for rare diseases was stated to be methods for attenuating financial burden [587]. It has been interpreted that, in the absence of the ability to confidently predict a robust and enduring treatment effect due to the lack of high quality, comparative and long-term data, one of the few options open to HTA decision-makers is reducing cost or using alternative financing strategies.

Value frameworks and ICER thresholds

Finally, included articles examined the value frameworks, and value assessment frameworks for rare diseases [550, 582, 584]. Blonda et al (2021) presented the use of different value assessment frameworks across European countries [550]. These VAFs included: standard economic evaluations; applying a variable ICER threshold based on societal preferences or other criteria; weighting QALYs based on societal preferences and applying a standard ICER threshold; applying a MCDA; and applying a separate VAF (such as assessing drugs through a different scheme, like the HST process used by NICE). However, while treatments must meet eligibility criteria for different VAFs (such as QALY weighting and being assessed through the HST process), the justification for the alternative VAF or the eligibility criteria is often missing.

An example of this is the HST programme. NICE evaluates ultra-orphan drugs via the HST programme, in which it permits ICER thresholds of between GBP100,000 to GBP300,000 per QALY. This is in stark contrast to non-HSTs which are required to achieve an ICER of between GBP20,000 and GBP50,000. Charlton (2022) notes that while there are eligibility criteria for NICE's HST programme, there is no clear reason for permitting a higher ICER threshold for ultra-orphan drugs compared with non-ultra-orphan drugs [582].

Broader value frameworks, involving carers and other non-health related impacts of a disease, may be reasonable to include in the assessment of diseases, including some rare diseases, with high impacts in these domains. However, the justifications for applying alternative value assessment frameworks specifically for rare diseases are unclear from the literature. It appears that deviations from a standard VAF in the appraisal of orphan treatments may not be based on a fundamental difference between orphan treatments and non-orphan treatments, but rather reflect a mechanism by which more costly treatments can be reimbursed. Articles in the literature did not identify clear justifications of why higher ICERs or prices are acceptable for orphan drugs, and in some cases (while not disagreeing with the higher threshold), questioned the basis for higher ICERs.

Both Charlton (2022) and Ollendorf, Chapman and Pearson (2018) highlight that, to achieve transparency and procedural fairness, adequate detail of the factors taken into account by decision makers is required [582, 584].

Although the literature has argued for broader value frameworks to capture the full value of rare diseases, most of the elements described in the value frameworks are not unique to rare diseases. NICE applies the following framework to the evaluation for highly-specialised therapies:

- Nature of the condition, including impact on patients and caregivers;
- Impact of the new technology, including health benefits and robustness of evidence;
- Budget impact, both broadly and specifically on the budget for specialized services;
- Impact of the new technology beyond health benefits, including elements outside the National Health Service and personal social services;
- Impact of the new technology on the delivery of specialized services, including staff training needs.

This framework for evaluation is broader than a health system perspective, however, there is no clear reason why rare diseases should be evaluated using a broader framework, and no clear elements within the framework that would not apply to non-rare diseases.

However, if the goal of society is not simply to maximise health gains but to fairly allocate health gains, this may mean that all patients should receive some chance at a health gain, even if purchasing that health gain might not be considered cost-effective [584]. Such a point of view, if held, should be tested amongst the population.

ADVANCED THERAPY MEDICINAL PRODUCTS

No guidance on the evaluation of technologies with limited data on long term outcomes was noted on any HTA website, except when applied to orphan drugs for rare diseases.

Two jurisdictions, both Canadian, are proposing time-limited reimbursement recommendations for emerging technologies with continually emerging evidence, which would be contingent on a future reassessment of additional evidence that addresses the uncertainties with the comparative clinical benefit and cost-effectiveness of the technology. No other jurisdictions provided any guidance on the evaluation of technologies with limited data on long term outcomes, except when applied to orphan drugs for rare diseases.

Gene and cell therapies, such as onasemnogene abeparvovec-xioi (a gene replacement therapy for spinal muscular atrophy) and Tisagenlecleucel (a chimeric antigen receptor

treatment for B-cell acute lymphoblastic leukaemia) are commonly categorised as ATMPs.

Advanced therapy medicinal products have presented some challenges to HTA for reimbursement decisions. Key challenges include [590]:

- The assessment of clinical effectiveness and safety
- *The extrapolation of effects beyond the trial duration*
- *The valuation of health outcomes*
- *The estimation of costs*
- *The selection of discount rates*
- The incorporation of equity considerations
- *Affordability*

For the purposes of this paper, only methods for addressing clinical concerns of ATMPs are discussed. The italicised items in the list above represent issues for the economic evaluation of ATMPs.

Assessment of clinical effectiveness and safety

As ATMPs tend to target rare diseases, the evidence is commonly based on small sample sizes [537, 607], non-comparative studies [537], heterogeneous populations with variable clinical courses and baseline characteristics [537, 608], and the use of surrogate endpoints that are often difficult to validate [537, 609]. The challenges of assessing the effectiveness of ATMPs is highlighted in a review of 3 European countries HTA decision making on 12 ATMPs that have been authorised for use in Europe that reported considerable differences in the estimate of added benefit of [592].

Another key issue with evidence of ATMPs is that most studies to date are based on very short term data, yet the effectiveness claim for the ATMP may be very long term [594]. In a systematic review published in 2022, including 72 studies of ATMPs, the longest follow up was identified as a median of 15.4 months for axicabtagene ciloleucel in the ZUMA-1 study [594]. The systematic review also noted that surrogate endpoints were frequently used in pivotal trials for ATMPs. Therefore, the evidence generated for ATMPs often requires considerable extrapolation and the translation of surrogates. The validation of surrogates has been discussed in 0.

Single-arm studies are common for ATMPs, partly because of the difficult in enrolling patients with life-threatening diseases into randomised studies [594]. Methods for addressing challenges with non-comparative studies has been discussed in 0.

Incorporating broader value elements into the assessment of ATMPs or for rare diseases is discussed in 0. One particular concept that may be unique to curative therapies is the value that may be associated with a single treatment vs a chronic treatment.

The literature did not identify statistical methods for reducing uncertainty relating to small sample sizes or heterogeneous populations or disease trajectories. Therefore,

HTA processes must either adjust the evidence requirements for ATMPs (or rare diseases) or adjust the reimbursement process [517, 536, 591, 610, 611], or both. Multiple reimbursement mechanisms have been proposed, including managed entry agreements, annuity (where payments are spread over time) [537, 538], pay-for-performance [536-538] or a subscription-style payment that involves unlimited treatments for a population based on a single sum [517]. A systematic review of ATMPs identified that outcome or performance-based payments were the most common reimbursement methods used by payers [594]. Coyle et al (2020) propose that adjusting the reimbursement mechanism may be more appropriate as, depending on the type of reimbursement scheme, it would incentivise post-launch evidence generation [517].

Ongoing evidence generation should ideally be timely RCTs (as proposed for the Cancer Drugs Fund in the UK [612]) or carefully designed RWD collection [536, 591]. To increase the likelihood that evidence is collected following reimbursement, Germany mandates the development of registries when the Federal Joint Committee considers RWE generation necessary [517]. A systematic review including 72 studies of ATMPs noted that, although HTA bodies are increasingly requesting post-launch collection of evidence, mechanisms and infrastructure required for data collection remain in development [594]. Furthermore, no standard framework currently exists for outlining the requirements for RWE [540]. For rare diseases, data collection should ideally be coordinated across jurisdictions.

In general, challenges associated with the assessment of the clinical benefit associated with ATMPs are almost entirely associated with their use in rare diseases, rather than characteristics of the technology itself. Although it has been argued that some ATMPs (such as gene therapies) are unique as they provide a one-off treatment that may result in a cure, this is not necessarily a barrier to HTA. Many health technologies are delivered once with lifelong effects. An example includes the use of direct-acting antivirals for hepatitis C virus. A brief course of treatment removes the virus, and has lifelong effects.

Therefore, it is not the nature of the technology, but the populations it is used to treat (and the evidence that is able to be generated), that results in a challenge for HTA agencies. While many recommendations have been published to overcome challenges with surrogate endpoints, single arm studies and quantifying uncertainty, most proposed methodological solutions do not markedly increase certainty at the point of decision-making[595], and HTA agencies are mitigating risk with alternative payment mechanisms and/or requiring ongoing evidence generation. However, HTA agencies must accept some additional methods to enable an initial value estimate of ATMPs.

HIGH-COST TREATMENTS

One study identified 122 ultra-expensive drugs currently funded in the US, and presented their therapeutic benefit ratings assessed by HTA agencies in France, Canada and Germany. The study found that approximately 75% of the drugs received a low added therapeutic benefit rating[597]. This finding may indicate that the pricing of costly

drugs in the US, where HTA is less prevalent, appears to be poorly correlated with benefit as assessed by HTA agencies.

HISTOLOGY-INDEPENDENT (TUMOUR AGNOSTIC) TREATMENTS

Two articles were identified that discussed frameworks for the evaluation of histology-independent (otherwise known as tumour-agnostic) therapies [598, 600].

Key challenges in the HTA of histology-independent therapies include [598, 600]:

- The use of basket trials (trials involving multiple histologies, commonly with few patients in each basket) and lack of comparative studies
- High uncertainty related to small sample sizes
- The inability to identify and quantify benefits of standard of care when historical studies do not present information on the presence or absence of the biomarker
- The inability to perform adjusted indirect comparisons if evidence of a comparator is available
- Difficulty in determining the appropriate comparator
- Uncertain estimate of patient numbers (due to uncertain prevalence of biomarker) and which results in uncertain cost of treatment.
- Uncertain estimate of testing uptake.

The use of basket trials for histology-independent treatments may reflect earlier stages of drug development, and subsequent RCTs may be feasible. However, in some cases, RCTs for some of the histologies included in the basket trial will not be possible due to the rarity of the biomarker in a particular histology [598]. Regulators have recently approved histology-independent treatments on the basis of basket trials (FDA approved pembrolizumab for microsatellite instability high or deficient mismatch repair positive solid tumours in 2017). Regulatory approval is likely to affect future confirmatory evidence typically required by HTA agencies.

Evaluation challenges associated with basket trials relate to the lack of randomisation (although study design is evolving to permit randomisation), the use of response rate as the primary endpoint, immature follow-up for PFS or OS, and small sample sizes. Currently, there is no standard HTA approach to the evaluation of histology-independent drugs, which has resulted in differences in HTA recommendations. Larotrectinib was not recommended in Canada, but was recommended with a managed access program in England [598].

As histology-independent studies involve heterogeneous populations with different prognoses, it may not be meaningful to pool progression-free or OS. Therefore, trials report on response rates. This raises the challenge of whether response rates are adequate surrogates for establishing benefit. A discussion of surrogate endpoints is included in 0.

Gaultney et al (2021) propose the use of RWD to create a propensity-matched external control arm [598]. However, they acknowledge that the success of such an approach will be contingent upon the availability of data, ability to match, and may be undermined if the prognostic effect of the genetic mutation is unknown. The authors also recommend the use of intra-patient comparisons (before/after comparisons, using a prior line of therapy as a control) [598]. However, such an approach is unlikely possible for an HTA agency to perform unless data have been collected at the time of the recruitment to the basket trial. Further, there is a risk that the application of prior lines of therapy may be truncated if a patient is seeking access to a study treatment. Generation of historical or external control arms is discussed in 0.

Schiller et al (2023) reported on the results of expert interviews with 7 participants and a literature review including 23 reports and 8 HTAs [600]. The solutions identified in the study included the use of RWE, cooperation among stakeholders, division of the indication, generation of evidence of the transferability to the target healthcare system, weighting of historical controls, conditional decisions (and reassessments) and improvements to the design and analysis of basket studies. The authors acknowledge that no direct solutions were identified for many of the challenges associated with the assessment of tumour agnostic therapies.

One article was identified that discussed the French National Authority for Health guidance for the assessment of basket trials [599]. The statement included the following recommendations:

- Randomisation (where possible)
- Indirect comparisons only if a direct comparison is not possible, and an external control group is prespecified
- Stratification of the basket trial should occur by tumour location
- Minimum of 30 patients per cohort
- Appropriate comparators are used
- Clinically relevant endpoints
- Joint evaluation of the companion diagnostic test
- Documentation on the prognostic value of the genetic alteration

The authors noted that the use of basket trials do not substantially alter the methods used by HTA agencies to obtain quality evidence on the efficacy and safety of a proposed technology, and do not justify a change in the methodological requirements by the French National Health Insurance Fund.

An unpublished guidance document for preparing submissions for biomarker guided therapies for tumour type agnostic cancer was prepared by AHTA. A summary of the approach is described below.

Biomarker guided therapies can be used across multiple tumour types, however the evidence available for each tumour type may vary. It is not possible to evaluate the effectiveness of all tumour types in aggregate for two reasons:

1. Response rates are not adequate for establishing effectiveness. The translation of response rates to patient relevant outcomes will differ by tumour type. Progression-free or OS will differ across tumour types.
2. As the incremental effectiveness will differ across tumour types due to biology or available alternative therapies, the use of aggregated outcomes across all tumour types would assume that the selection of tumour types in the basket trial represents the distribution in the target population.

The approach proposes splitting the basket study into categories of tumour types.

- Independent tumour type: a tumour type included in a basket study that is assessed by itself (an example is pembrolizumab for MSI-H / dMMR advanced or metastatic colorectal cancer).
- Representative tumour type: a tumour type intended to act as a proxy for the estimate of effectiveness, safety and cost for a tumour group (including representative tumour types and dependent tumour types).
- Dependent tumour type: tumour types within a tumour group that rely upon evidence from a representative tumour type.
- Others not otherwise categorised: tumour types have sufficient evidence to indicate that there is likely to be some clinical benefit, but the magnitude cannot be established (and the tumour type cannot be grouped into a tumour group).

Requirements of the approach include an estimate of the size of the testing and treatment populations for each tumour type, and the reporting of other known biomarkers (onco-drivers) in each of the tumour types.

There are three approaches that are anticipated to be used in combination with each other.

1. Independent tumour type approach

This is the assessment of a tumour type on its own merits. The assessment would follow the approach in the PBAC Guidelines, including PT4 (co-dependent product type). The economic analysis undertaken to inform value would include the number need to test to estimate the cost of testing in the subgroup.

2. Representative tumour type approach

To avoid the need to generate incremental evidence for each tumour type (which increases complexity and reduces certainty in an evaluation), a tumour group with similar tumour types can be created. The premise of the tumour group is that included tumours have a similar absolute benefit. This is established if:

- Tumours have a similar prognosis (i.e., survival following the use of the comparator); and,
- The response rate to the proposed medicine is similar.

Each tumour group would have a representative tumour type, which will be used to inform the effectiveness and cost-effectiveness of the group. The focus of consideration for the representative tumour type approach is to justify group membership. Where group membership is not well justified (either there is a lack of evidence to support a similar prognosis or similar response rate, or there is evidence that the response rate clearly has a different impact on survival), the representative approach is less likely to be acceptable.

While the clinical assessment of the tumour group relies upon an assessment of the incremental effectiveness of the representative tumour type and the most relevant comparator, the economic evaluation of the group requires an estimate of the weighted cost of comparators across the group to inform incremental costs.

3. Non-quantifiable benefit approach

This approach is intended to provide access to a treatment in a group with high unmet clinical need. It requires evidence to support that the treatment of the tumour type with the proposed medicine in the proposed line results in net benefit. However, the approach is used when no magnitude of benefit can be reliably established. The approach may be supported by intermediate outcomes (such as response rates) and supplementary evidence such as biological plausibility.

The economic approach assumes that there is no additional benefit, but there is additional cost.

Each of these approaches are incorporated into a stepwise economic evaluation in which the incremental benefits and incremental costs are added. In the example table below, the independent tumour type A results in no additional benefit (i.e., it is noninferior to the comparator), but at the asking price it is cost-saving. Tumour group B is results in an incremental benefit and is less costly. The next 5 assessments are more effective but more costly. The final group shows some response rate, but no evidence of incremental benefit can be established, and only costs are incorporated into the analysis. Table 65 presents a hypothetical example of the proposed approach. Figure 32 represents the stepwise ICER on a cost-effectiveness plane.

Table 65 Cumulative cost-effectiveness analysis of a histology-independent technology

Tumour type / group	Incremental Cost	Incremental Benefit	ICER	Relative proportion in group	Cumulative ICER
Independent tumour type A	-$22,000	0	Cost Saving	12%	Cost Saving
Tumour group B	-$4,000	0.8	Dominant	8%	Dominant
Tumour group C	$14,000	0.7	$20,000	18%	Dominant

Independent tumour type D	$31,000	0.4	$77,500	22%	$22,950
Tumour group E	$54,000	0.4	$135,000	15%	$42,840
Tumour group F	$59,000	0.4	$147,500	9%	$52,914
Independent tumour type G	$45,000	0.2	$225,000	10%	$61,650
Non-quantifiable benefit t-type H	$55,000	0	Costs only	6%	$70,025

ICER = Incremental cost-effectiveness ratio (cost per additional quality adjusted life year).

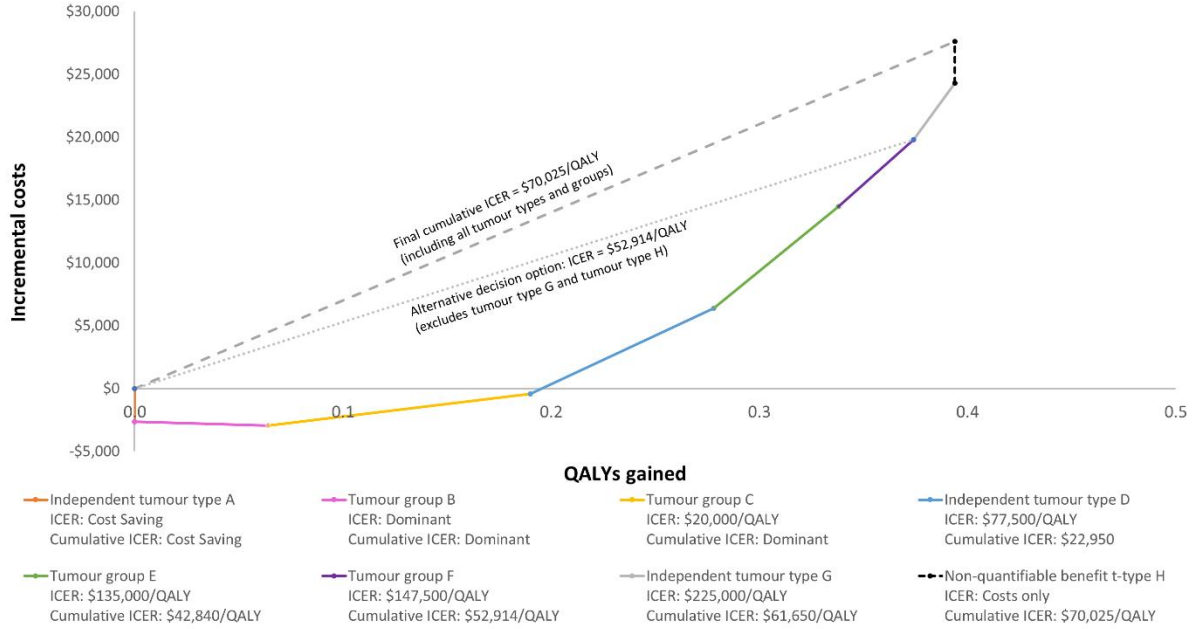

Figure 32 Cumulative cost-effectiveness plane for a histology-independent technology

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

There are several benefits to this approach:

1. Tumour types with adequate evidence can be evaluated independently, or be used as a proxy (representative tumour type) for a group.
2. Tumour types that have similar prognoses (without the treatment) and similar response rates to other tumours, but where there are small numbers or less certain comparative evidence, can leverage the evidence from representative tumour types.
3. Tumour types for which the prognosis is highly uncertain, and no credible magnitude of treatment can be established, can be retained in the analysis.
4. Individual tumour types that are not likely to be regarded as cost-effective may still be recommended as the overall ICER, once pooled with other tumour types, may be acceptable.

Such an approach permits a positive recommendation for a broad range of tumour types for a histology independent treatment. The financial risk is shared between the manufacturer and the payer, as the price of the treatment must be low enough for the

treatment to be cost-effective *in totum*, but permits some histology groups to be non-cost-effective.

Limitations of this approach arise if some groups are clearly non-cost-effective and the histology independent treatment becomes standard of care, after which, new treatments for that group may apply the costs and benefits of the histology independent treatment as a comparator. In this circumstance, the cost-effective price of the histology independent treatment would have to be established.

ANTIMICROBIALS AND VACCINES

Four studies were identified in the scoping review that discussed methodology for the appraisal of antimicrobials, and two studies discussed the appraisal of vaccines.

Schurer et al (2023) reported on the market failure of new antimicrobials and learnings from a Swedish pilot scheme and the NICE subscription-style payment model [335]. The authors indicate that there is a lack of financial incentives for manufacturers to invest in new antimicrobials, partly because current HTA methods fail to capture the full value of antimicrobials. New antimicrobials are likely to be used uncommonly once developed, to limit antimicrobial resistance. As utilisation is low, reimbursement would typically also be low. Recent commentary has called for incentives that at least partially delink the payment for antimicrobial agents from their sales volume [177, 366, 613, 614].

The Public Health Agency of Sweden (PHAS) started a pilot scheme in 2018 which intends to partially delink the payment for antimicrobial agents from sales and guarantee supply. The scheme provides manufacturers who participate with a minimum annual revenue of SEK4 million or 10% in addition to sales, whichever is higher.

NICE is testing a payment model for fully delinking payments from sales volume. The model offers manufacturers an annual fee to have on-demand access to the antimicrobial agent. The subscription fee is based on the value of the product as assessed through an adapted HTA process. The HTA process considers additional elements of value, including spectrum value (the replacement of broad spectrum with narrow spectrum antimicrobials), transmission value, enablement value (the value of permitting other treatments to take place), diversity value (the value of treatment options) and insurance value. The evaluation process also departs from the use of an ICER for an individual, but rather estimates a population wide QALY gain. Schurer et al (2023) reported several challenges for the assessment of antimicrobials [335]. The results of the economic analysis were deemed insufficient for decision-making, and NICE was required to employ assumptions, and applying arbitrary adjustments, to estimate the value of the antimicrobials.

The value elements identified by NICE were partly reported by Hillock et al (2020) [601]. The authors interviewed 18 stakeholders representing manufacturers and policymakers regarding whether the Australian HTA framework adequately captures the unique attributes of antimicrobials [601]. Participants indicated that the current HTA process does

not recognise the value of narrow spectrum antibiotics (for preserving the use of broader spectrum antibiotics, and reducing the likelihood of antibiotic resistance), nor the recognition that the use of antibiotics permits the use of other treatments (like treatment of patients with cancer, in whom infections are common and life-threatening). Participants noted that comparators are often inexpensive, which reduces the prices that can be sought for new antimicrobials, and disincentivises the production of generic antibiotics. Decisionmakers also identified that there is additional value in guaranteed supply.

Gotham et al (2021) reported on methods for funding antimicrobial treatments in Sweden and UK (both discussed above), France, Germany, and the USA [177]. The US has multiple current or proposed policies that provide extended market exclusivity, guaranteed revenue, and ensure stable supply. Other than the approach taken by NICE, none of the mechanisms appear to involve a method for establishing the specific value of antimicrobials to inform price, and therefore sit outside the HTA process.

Morton et al (2019) identifies additional benefits and costs that should be incorporated into the assessment of antimicrobials [367]. These broader value elements include:

- The benefits and costs of using the antimicrobial to the individual
- The benefits and cost-savings associated with the reduction in the transmission of disease
- The value and cost-savings associated with the preservation of existing antibiotics (by avoiding antimicrobial resistance)

The authors offer an example of the inclusion of broader value elements for a hypothetical antimicrobial. Incorporating a reduction in the transmission of disease (by 40% in their example) results in an ICER that is markedly reduced. It is unclear how applicable the hypothetical evaluation is to many antibiotic resistant bacteria that are common in the population, such that a new antimicrobial agent is unlikely to markedly reduce transmission. The proposed approach, were it able to be informed by credible evidence, appears to better capture the value and costs of new antimicrobial agents.

Two studies discussing HTA of vaccines both reported on the need for a broader consideration of value [213, 413]. The proposed value elements (in addition to individual health effects) were consistent across both studies, and included:

- Comprehensive cost-offsets within the health care system
- Impact on care givers
- Impact on transmission / health of the unvaccinated population
- Prevention of antimicrobial resistance (both directly for vaccines against bacteria, or by reducing viral infections that are then inappropriately treated with antibiotics)
- Productivity, and macroeconomic effects (such as might occur with outbreaks)

PRECISION MEDICINE AND GENOMIC PROFILING

Seven jurisdictions considered the evaluation of codependent technologies. Five jurisdictions described the evaluation pathway for codependent technologies and two jurisdictions failed to provide any guidance. Three jurisdictions required a combined submission of the test and drug. NICE requires a sensitivity analysis without the cost of the diagnostic test. When appropriate, NICE also requests that the diagnostic accuracy of the test is incorporated into the economic evaluation.

Table 66 Methods for codependent technologies

Method	Purpose	Requirements/Assumptions/Limitations	Reference
A combined submission of the test and drug	A codependent submission is required when the Minister for Health requires advice from both the PBAC and MSAC.	The net clinical benefits of using both technologies need to be determined. The cost-effectiveness and financial implications of using both technologies are also required to form part of the reimbursement decision. Both direct and linked evidence are acceptable	Australia (PBAC) PBAC Guidelines (2016) [187]
Assessment of co-dependent technologies	Decisions on new codependent technologies require evidence on the clinical benefit in terms of patient health outcomes stratified according to biomarker status	In the absence of direct evidence provide linked evidence: The relative effectiveness of treatment versus control in a biomarker stratified versus a biomarker un-stratified population. Patients with discordant test results are randomised to treatment/control and compared to the RCT in an untested population. Retrospective analysis of biomarker status.	Austria (AIHTA) Procedural guidance for the systematic evaluation of biomarker tests (2014) [448]
A combined submission of the test and drug	The clinical utility of a diagnostic test must be demonstrated: the marker identified by the test must change the effect of the treatment; the treatment must be effective in marker (+) patients; the treatment must have no clinical benefit in marker (-) patients.	The demonstration of clinical utility of the diagnostic test is a prerequisite to the joint assessment of the codependent therapy	France (HAS) Methodological Guide: Companion diagnostic tests (2014) [445]
Inclusion of the associated costs of the diagnostic in the assessments of clinical and cost effectiveness	If a diagnostic test is required to support the treatment decision for the specific technology, the costs of the diagnostic test must be included in the assessments of clinical and cost effectiveness.	A sensitivity analysis, without the cost of the diagnostic test should be included along with the diagnostic accuracy of the test, when appropriate.	UK (NICE) NICE HTA manual (2022) [27]

AIHTA = Austrian Institute for Health Technology Assessment; HAS = Haute Autorité de Santé; HTA = Health technology assessment; MSAC = Medical Services Advisory Committee; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; RCT = Randomised controlled trial

Two articles were identified during the scoping review that discussed precision medicine and genomics.

Love-Koh et al (2018) reported emerging precision medicine based on 31 articles and the results of interviews with 13 experts [604]. The authors found that the use of precision medicine, particularly complex algorithms (based on machine learning), digital health applications, and biomarkers based on genomics, is likely to accelerate. The authors noted that HTA methods face multiple challenges. Key issues raised were:

- New tests (such as whole genome sequencing) may result in many treatment options over an individual's lifetime.
- More complex and variable treatment pathways (due to more targeted treatments) will result in considerable structural uncertainty in current decision-analytic processes.
- Many genomics tests may provide information for that does not directly alter treatment options, but provides information to individuals (value of knowing), the utility of which is unlikely captured in current HTA assessments.
- As tests and treatments become more targeted, obtaining head-to-head estimates of comparative effectiveness will become challenging.

The authors discuss in greater detail some of the concerns, but do not offer precise methodological or procedural solutions.

Tarride, Gould and Thomas (2020) also discuss concerns arising with the evaluation of precision medicine, particularly relating to comprehensive genomic profiling (CGP) [605]. The authors reviewed literature in oncology and held stakeholder interviews across countries using ICERs as part of HTA. The study reported four key concerns with current HTA frameworks for the evaluation of comprehensive genomic profiling:

- Diagnostic tests are usually evaluated with paired therapeutic interventions. CGP links a single test to multiple treatments. The authors note that, in lung cancer alone, more than 12 genomic biomarkers have been identified that may target treatment. As with Love-Koh et al (2018), the authors identified that as genetic testing increases to encompass multiple targets for multiple therapeutic interventions, the assessment complexity of CGP will increase [604].
- Genomic testing may also provide personal utility (such as value of knowing or value of hope), and systems benefits (such as increased diagnostic accuracy).
- CGP may improve patient participation in clinical trials.
- As greater numbers of targetable biomarkers become known, the value of CGP increases.

To address some of the identified limitations in the HTA frameworks for the evaluation of genomic testing, Tarride, Gould and Thomas (2020) [605] propose:

- Greater investment in genomic testing infrastructure
- Decoupling the value assessment of diagnostic testing and treatments
- Including broader value elements into the assessment of CGP (value frameworks for precision medicine are discussed in 0).

- Use alternative funding mechanisms, such as block funding for the initial procurement of platform infrastructure (similar to Radiation Oncology Health Program Grants)
- Mandate the collection of a minimum RWE dataset to facilitate the assessment of clinical and cost-effectiveness of CGP over time.

METHODS ARISING FROM RECENT REFORMS AND ADDITIONAL METHODS IDENTIFIED IN THE SCOPING REVIEW

RECENT REFORMS

HTA Agency websites from the included jurisdictions were searched to identify recent reforms to HTA processes.

Documented recent reforms were identified on HTA agency websites for seven jurisdictions. The topics of reform included:

- Real-world evidence (NICE, CADTH, AIHTA)
- Early access for medicinal products (CADTH, IHE, AIHTA)
- Patient involvement in HTA (EUnetHTA, KCE)
- Professional healthcare worker involvement in HTA (EUnetHTA)
- Equity in health (US ICER)

A brief description of the reforms is provided in Table 67. None of these reforms represent a new or innovative approach that has not yet been used in HTA assessment in at least some jurisdictions. Overall, the reforms were not initiated by the recognitions of changing technologies. Rather they result from the recognition of the need for expediated availability of new effective treatments and the requirement for a fair and equitable health care service.

However, it is by no means certain that all reforms have been identified for all jurisdictions examined as it is possible that not all HTA reforms are listed on the websites.

Table 67 Methods arising from recent reforms

Country	Organisation	Recent reform	Date of reform proposal	Reform evaluated	Basis of Reform
UK	NICE	Real-world evidence framework [170]	June 2022	The use of RWD to resolve gaps in knowledge and promote access to innovative medicines for patients	As described in the NICE 5-year transformation plan
Canada	CADTH	Time-limited Reimbursement Recommendations [443]	March 2023	To modernise the terms and conditions associated with approvals based on early-phase clinical data	Global regulatory authorities are developing processes to enable faster and more agile review of promising medicines.
		Real-World Evidence (RWE) framework [427]	April 2023	The RWE Steering Committee investigated the use of RWE in regulatory and reimbursement decision-making.	The need to develop knowledge, capabilities, and competencies related to RWE to meet this challenge of evaluating drugs for the treatment of rare diseases
Alberta, Canada	IHE	Life-cycle (LC)-HTA framework [615]	February 2022	A national strategy to balance equitable access to high-cost drugs for rare diseases with a sustainable healthcare system.	In response to the increasingly limited safety and efficacy evidence for drugs and the need for new approaches to evaluation.
Europe	EUnetHTA	Patient Input in Relative Effectiveness Assessments [566]	May 2019	To develop recommendations for direct patient input into the EUnetHTA Relative Effectiveness Assessments process.	The EUnetHTA Task Group on Patients and Consumers and Healthcare Providers was established in 2017 in response to the importance of involving stakeholders in HTA and decision processes.
		Healthcare Professional Involvement in Relative Effectiveness Assessments [616]	April 2020	To develop recommendations for Healthcare Professionals involvement in the EUnetHTA Relative Effectiveness Assessments process.	
USA	US ICER	Methods that Support Health Equity [617]	March 2023	To develop recommendations to improve the consideration of health equity within the HTA review processes.	To advance society's goal to improve health equity for racial, ethnic, and other socially disadvantaged groups.
Austria	AIHTA	Improving patient access to ATMPs [449]	January 2020	To provide potential solutions to improved access to advanced medicinal products for patients with rare diseases.	The RARE IMPACT Working Group, a multi-stakeholder initiative aimed at improving patient access to gene and cell therapies.
		Models for using RWE for public funding of high-priced therapies [618]	2021	To launch new reimbursement models with data generation of innovative drugs for early access schemes.	To provide effective, safe, and equal access to innovative medicines and maintaining financial sustainability for the healthcare system
Belgium	KCE	Patient Involvement in KCE Research [109]	April 2021	To generate a series of recommendations for patient involvement in health policy research into practice.	The sway of ethical and procedural rationale for patient involvement in health policy research.

AIHTA = Austrian Institute for Health Technology Assessment; ATMPs = Advanced therapeutic medicinal products; CADTH = Canadian Agency for Drugs and Technologies in Health; EUnetHTA = European network for Health Technology Assessment; IHE = Institute of Health Economics; KCE = The Belgian Health Care Knowledge Centre; LC-HTA = Life-cycle health technology assessment; NICE = National Institute for Health and Care Excellence; RARE IMPACT = A consortium of manufacturers of gene and cell therapies and umbrella organisations such as the European Federation of Pharmaceutical Industries and Associations (EFPIA) and the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE); RWE = Real world evidence; UK = United Kingdom; USA = United States of America; US ICER = US Institute for Clinical and Economic Review.

ADDITIONAL METHODS

There were additional methods identified during the scoping review that were deemed unlikely to address key themes of the HTA review.

Table 68 Studies presenting additional methods not considered in depth in this Review

Reference	Description	Reason for not considering in depth
Alshreef et al (2019) [619]	Adjustments to treatment effectiveness for patient non-adherence	May improve precision of estimates of treatment effect. Many methods difficult to validate without access to IPD.
Angelis, Lange and Kanavos (2018) [620]	Comparison of HTA methods and processes across European countries	Information already captured by grey literature search
Chassany et al (2022) [351]	Describes the need to harmonise PROM evidence across jurisdictions	While HTA agencies may request methods for patient reported outcomes, the study relates more to evidence generation than methods for evaluation.
Dankó, Blay and Garrison (2019) [621]	Description of challenges for the assessment of targeted combination therapies	Describes concepts associated with the difficulties of assessing and funding combination therapies but do not outline clear methodological solutions.
Esandi et al (2019) [622]	Framework for identifying low value technologies (disinvestment)	Not specifically addressing the stated aims of the review.
Monnickendam et al (2019) [623]	Measuring survival in the presence of nonproportional hazards	Nonproportional hazards are a common concern during HTA. The authors suggest the use of RMST. While nonproportional hazards may undermine the interpretation of hazard ratios, Australian HTA agencies typically use economic modelling that applies the KM curve directly, and therefore nonproportional hazards do not impact the assessment of cost-effectiveness.
Morga et al (2023) [624]	Alternatives to the ITT principle of evaluating clinical trials	Currently, the PBAC Guidelines describe alternatives to the ITT approach, including options to present adjustments for treatment-switching, and subgroup analyses.
Rejon-Parrilla, Espin and Epstein (2022) [625]	How HTA can define and reward innovation.	The report includes how 5 countries value innovation. In three cases (France, Japan and Italy), innovation is captured as disease severity, unmet need and added therapeutic value. England and Spain consider innovation as a separate value element. Innovation is not well defined, and even England appears to define “innovation” as requiring characteristics that would also imply that the technology is addressing an unmet need.
Unkel et al (2019) [626]	Analysis of safety of treatments with different follow up times	May provide guidance on better estimating the safety profile of a technology where the intervention arm has substantially more follow up than the control arm for safety events. Not directly relevant to the Review goals.

HTA = health technology assessment; IPD = Individual patient data; ITT = intention to treat; KM = Kaplan-Meier; PROM = Patient-Reported Outcome Measure; RMST = restricted mean survival time.

IMPLICATIONS

SUMMARY AND OPTIONS

For the purpose of this review, studies discussing methods were included if they described approaches for the analysis of data (e.g., statistical analyses), described the type of data that may be relevant for decision making (e.g., value frameworks), or described methods for reducing uncertainty associated with limitations in the evidence.

The literature review included 142 articles and incorporated an additional 32 articles from reference lists or targeted searches. Identified methods were placed into one of four categories:

- Assessment of nonrandomised and observational evidence
- Assessment of surrogate endpoints
- Value frameworks and MCDA
- Assessment of specific populations and technologies

DIFFERENCES AND SIMILARITIES BETWEEN HTA METHODOLOGIES USED IN AUSTRALIA AND IN OTHER INTERNATIONAL JURISDICTIONS

A comparison of methods used in Australia with the 20 international jurisdictions where information was available (including recent reforms) identified only a few differences. In Australia, guidance for writing HTA reports for assessing the clinical effectiveness of medicines is provided in the *PBAC Guidelines* [187], whereas the guidance for highly specialised medicines (e.g., cell-based treatments) is in the *MSAC Guidelines* [290].

Not all HTA agency websites had copies of, or links to, guidelines that outlined how they would conduct an assessment or evaluation of a medicine. Some agencies had guidance documents that outlined the procedures for only a few aspects of the evaluation process, such as how to incorporate consumer evidence or nonrandomised studies into the evaluation.

The methods arising from recent HTA reforms undertaken by agencies were centred around a recognition of the need for expedited availability of new effective treatments and the requirement for a fair and equitable health care service. These reforms included:

- Real-world evidence (NICE, CADTH, AIHTA)
- Early access for medicinal products (CADTH, IHE, AIHTA)
- Patient involvement in HTA (EUnetHTA, KCE)
- Professional healthcare worker involvement in HTA (EUnetHTA)

- Equity in health (US ICER)

None of these reforms represent a new or innovative approach, as these have been addressed in HTA in other jurisdictions. However, it is by no means certain that all reforms have been identified for all of the jurisdictions examined.

Overall, the guidance provided for conducting and evaluating HTA reports in the *PBAC Guidelines* are predominantly on par with most other international jurisdictions, with some notable exceptions. The *PBAC Guidelines* could provide additional guidance on the use of RWE, consumer evidence and equity in health.

PROPOSED OVERARCHING PRINCIPLES OF METHODOLOGY REFORM IN AUSTRALIA

Value based medicine involves a method of pricing health interventions based on patient and societal value, and this approach is adopted by most developed countries involved in HTA. Value based medicine results in the dual responsibilities for the decision-maker: to deliver health to patients; and, to deliver value to society that shares limited health resources. Core to the estimate of value are two components:

1. An estimate of incremental benefit across relevant value elements, as well as some characterisation of uncertainty in this estimate.
2. An understanding of what constitutes a cost-effective use of resources, and how different value elements might modify this understanding.

Notwithstanding delays to access, an 'ideal' pathway for valuing technologies involves a highly certain estimate of added benefit across relevant value domains. The most influential value domains across countries are incremental clinical effectiveness (added benefit) and the related estimate of cost per unit of effectiveness (often cost per additional QALY). Incremental effectiveness is ideally generated by low risk of bias evidence, such as applicable randomised controlled trials.

There are circumstances where an 'ideal' evaluation pathway is not possible. These circumstances include: when an RCT is not possible to conduct; when an RCT may be forthcoming but may result in a delay in decision making; when considering only clinical effectiveness may be insufficient to capture important impacts of a technology in other value domains. Methodologies have evolved over time to equip decision-makers with tools and evidence that enable informed decisions in the absence of low risk of bias RCTs. As there is a trend for regulatory approval based on earlier or less mature evidence dossiers, and with the increased attention on technologies for rare diseases, there is a need to consider methodologies that ensure timely access to new technologies in the absence of 'ideal' evidence.

While many methods were identified in the Review of methodologies, two key themes emerged from this Review that may provide an opportunity for decision-makers. These are:

- Methods for estimating the incremental clinical benefit in the absence of randomised controlled trials; and,
- Methods for incorporating value elements beyond incremental effectiveness into deliberation.

In some cases, more complex methods for generating treatment effects in the absence of RCTs may reduce confounding associated with simple methods, and in other cases, may permit a comparison where one was not previously possible. However, more complex methods may also involve a trade-off between improved estimates, and both transparency and the ability to validate the results.

This review has identified that there are opportunities to incorporate methodologies into HTA that may facilitate earlier access to technologies, or more complete estimates of value. To support the adoption of specific methods, options are presented throughout this section. However, several conditions for the successful implementation of methods are common across most options and are presented below as overarching principles of methodological reform in Australian HTA.

Principles for adopting methods in Australian HTA

1. Maintain a preference for high quality evidence, if available.

Decision-makers should maintain a preference for high quality, *applicable* sources of evidence with low risk of bias, including randomised controlled trials, over lower quality and less certain evidence. Australian HTA guidance should request justifications for not providing high-quality evidence, and request whether better quality evidence is pending, or is unlikely to be generated in a timely manner.

2. Use fit-for-purpose, transparent methods that are only as complex as required to address the problem.

Fit for purpose methods that maintain transparency (including the ability of an evaluation group to replicate the results) should be preferred over methods that cannot be validated. Simpler methods, where fit-for-purpose, should be preferred unless more advanced techniques can be demonstrated to provide a clear and substantial advantage. Limitations of some simple methods are well understood, and the presentation of simple methods alongside narrative descriptions of the likely direction of bias may be as informative as more complex methods that reduce bias but also transparency.

3. Justify the use of more complex methods.

The use of more complex methods in the estimation of incremental clinical effectiveness should be justified. Justification should refer to the advantages of the method (for example, a reduction in confounding or the ability to estimate long term outcomes) as well as trade-offs (for example, inability to validate the results, greater evaluation burden, greater uncertainty). The motivation for the use of a method should align with the goals of better informing decision makers and enabling more rapid access of effective technologies to patients.

4. Develop guidance for methods in Australian HTA

Generate a curated list of methodologies that are preferred by decision-makers, in collaboration with evaluation groups and sponsors. For each method in the list, create a brief guidance paper that includes the following:

a. Description of the method including links to key peer-reviewed articles
b. Guidance for sponsors or evaluation groups on the presentation of the method and results in a submission or assessment report (including a checklist of what data may be required to validate the method) with the goal of ensuring transparency
c. Guidance for evaluation groups on how to evaluate the results generated by a method, and how to present uncertainty and the impact of the uncertainty on risk faced by decision-makers
d. Brief explanation for the decision-making committees about how to interpret the results derived by a method
e. Brief explanation of the method for the benefit of consumers

Guidance documents (which may be developed by the Department, HTA groups or other experts) would be similar to the technical support documents developed by the NICE Decision Support Unit. The guidance documents should be reviewed by experts, made available to stakeholders in a common repository, and updated when required.

5. Provide training and guidance to evaluation groups when adopting new methods

Feedback from key HTA evaluation groups in Australia indicated that training and guidance would be required to facilitate the adoption of new or complex methods. Training would ensure that the evaluation approach, the quality of the evaluation and presentation in the commentary is consistent across evaluation groups. Training focusing on the interpretation of results may be valuable for committee members.

6. Provide feedback to applicants and sponsors on their use and presentation of analyses based on more complex methods

Feedback on the quality of analyses, particularly relating to the adequacy of supporting data and assumptions, may facilitate continuous improvement in the quality of submissions. Methods that are not adequately reported in submissions (according to the developed guidance) should be identified early in the HTA evaluation and returned to the sponsor for further information.

7. Complex methods that result in estimates that are considerably uncertain may be more acceptable if paired with provisional funding pathways.

To make a decision regarding the cost-effectiveness of a technology, committees consider the uncertainty of the treatment effect. In circumstances of higher uncertainty, committees may consider more conservative estimates of the treatment effect, lower the ICER for determining cost-effectiveness, or may seek to list subject to ongoing data collection or other managed entry requirements. Where methods are well established, adequately reported and transparent (able to be replicated by an

evaluation group), or the approach is conservative, a decision-maker may have the confidence to make a recommendation that does not require review. However, in some cases (not all), complex methods used to generate an estimate of incremental treatment effect will be prone to bias or confounding. Rather than implementing risk mitigation measures such as requiring conservative estimates, or price reductions, a committee may recommend a provisional listing with a planned review based on more robust, confirmatory data.

There are many methods described in this review that are able to provide a 'working estimate' of a treatment effect for the purpose of a provisional listing, but may not necessarily provide the certainty necessary for making a decision that is not subject to review. In some cases, the uncertainty arises from the data source (particularly for RWD) rather than the method.

The incorporation of provisional pathways into HTA processes was a feature of several publications identified in the Review. Provisional pathways, when paired with methods or data that generate uncertain estimates, were seen as a way of accelerating access to beneficial technologies in the absence of robust estimates of the magnitude of added benefit.

8. The acceptability of uncertainty in estimates may be greater in areas of high clinical need.

Complex methods may permit the generation of comparative estimates (in circumstances where there is a lack of comparative data), however may also result in considerable uncertainty. The acceptability of uncertainty may be greater if the impact of an uncertain estimate in treatment effect is outweighed by the clinical need of the technology, or in circumstances where higher quality data are not forthcoming (rare diseases). Where the clinical need is not high, delaying decision-making until higher quality evidence is available may be preferable.

ASSESSMENT OF NONRANDOMISED AND OBSERVATIONAL EVIDENCE

Multiple methods to facilitate the assessment of nonrandomised studies were identified in the scoping review and from the various jurisdictions. These included indirect comparison methods, curation of control arms (historical, external or intra-patient), frameworks for the use of observational evidence, and methods for the use of RWE.

Indirect comparisons

The scoping review identified 4 articles discussing indirect treatment comparison methods. Seven jurisdictions reported on specific methods for the indirect comparison of RCTs. The likely reason for the low yield of articles is that methods for ITC have been relatively stable over the last 5 years and the use of indirect comparisons to generate

indirect estimates of treatment effects is not new. An early approach was first described by Heiner Bücher in a publication in 1997 [460], and it continues to be used.

The Bücher ITC method is described as an 'adjusted' (herein referred to as 'anchored') indirect comparison because the indirect estimates of treatment effect are based on a 'common reference' arm present in the studies being indirectly compared. The Bücher method contrasts with unanchored indirect comparison methods in which randomisation between the treatment groups cannot be preserved [460]. The ongoing use and acceptability of the Bücher method in HTA is likely due to its simplicity. The method can be used to compare both binary and continuous outcomes and it can be applied to aggregate data with no requirement for IPD. As is the case for other ITC methods, the Bücher method assumes that the studies included in the ITC are similar with regard to the design, population, outcome measurements, and the distribution of treatment effect-modifiers (i.e., study/patient factors that have an independent influence on the treatment outcome). The Bücher method was reported to be a recommended method of all seven HTA agencies included in a review performed by Es-Skali and Spoors in 2018 [456](Table 38).

Additional techniques to indirectly compare treatments have been developed, in part to overcome some of the limitations of the simple pairwise indirect comparisons first described by Bücher. These include multiple treatment comparisons or network meta-analyses, as well as methods for adjusting indirect treatment effects to account for known differences in baseline characteristics (MAIC, or STC).

Table 69 Comparison of advantages and limitations of the Bücher ITC method and more advanced methods for ITC

	Pairwise indirect comparisons (Bücher)	Advanced methods
Advantages	Simple to perform and intuitive. Can be reproduced and verified by HTA evaluators (transparent). No IPD are required.	Permits comparisons using multiple trials with different comparators (MTC, NMA). Can adjust for differences in reported baseline characteristics (MAIC, STC). MAIC and STC may be used without a common reference arm.
Limitations	Unable to compare multiple studies with multiple interventions.	MAIC and STC require IPD. Not reproducible by HTA evaluators. Verification of the final model for MAIC and STC not possible. Greater submission and evaluation burden for NMA and complex MTCs. Requires judgement relating to the inclusion or exclusion of trials (NMA) or the covariates (MAIC, STC). The use of MAIC can be limited by loss of effective sample size due to the matching process.

HTA = health technology assessment; IPD = individual patient data; MAIC = matching adjusted indirect comparison; MTC = mixed treatment comparison; NMA = network meta-analysis; STC = simulated treatment comparison.

Although the Bücher method is the most transparent approach, as it is easily replicated during evaluation, it may produce confounded results if the trials included in the pairwise comparison differ on important patient or disease characteristics. Population matching approaches may help adjust for some of the confounding in the ITC, however,

such approaches may be less transparent. One option to improve the transparency of MAIC and STC methods is the provision of the full IPD dataset to HTA evaluators to permit validation of the matching. While MAIC and STC approaches may overcome some of the transitivity concerns with studies and the limitations of simple pairwise ITC techniques, they do not ameliorate the risk of confounded analyses, particularly where confounders are unmeasured or cannot be controlled for, as might be the case when comparing studies of different periods or across different health care systems.

Pairwise, MAIC and STC approaches are intended for simple comparisons, though can be extended for use in simple networks. Larger or more complex networks require different approaches, such as Bayesian NMA or MTC. In some jurisdictions, HTA decision-makers may place greater emphasis on the parallel assessment of multiple technologies, which may require more complex indirect comparison methods. Within the Australian context, the *PBAC Guidelines* request a comparison against a main comparator, stating that "a single comparator will be appropriate in most circumstances". There may be circumstances where there are multiple comparators available and it is difficult to identify a main comparator, such as disease modifying agents for rheumatoid arthritis, in which a more complex network may be informative, though not essential to the evaluation of a new entrant. Another case for the use of NMA may be post-market reviews of medicines used for a single indication.

Where the need for complex indirect comparison methods is unclear or absent, the disadvantages related to their use likely outweigh their advantages. For larger networks, the evidentiary requirements increase. To perform a NMA, a HTA report must justify the inclusion and exclusion of studies, assess the transitivity of the included studies, assess the risk of bias within each included study, present estimates of homogeneity and consistency within the network, and report multiple sensitivity analyses. Transitivity is violated when the anchor treatment and population differs systematically among the studies in the network, which is almost certainly the case where included studies span a considerable period.

There may be multiple sources of confounding within a network that are difficult to identify – such as study design, health system, or period in which the study was conducted. Therefore, the accuracy of an indirect treatment effect derived from a NMA may be impacted in ways that are not immediately apparent.

Difficulty in validating NMA or more complex approaches to ITC is likely the reason that HTA agencies, including PBAC, have stated a preference for simpler approaches, where possible.

In general, global HTA agencies either prefer or accept as reasonable the Bücher ITC approach for the comparison of two trials. For example, EUnetHTA (in 2015) noted that the Bayesian network meta-analyses are less advantageous than the Bücher ITC approach due to their complexity [515]. While guidance from EUnetHTA regarding indirect comparisons has been updated to reflect that NMA has become more acceptable, concerns relating to complexity remain. Not only is the Bücher method more

transparent, but with only two trials, or very small linear networks, the results are unlikely to differ from more complex NMA approaches.

Due to the risk of confounding associated with ITCs, the Scottish Medicines Consortium is more likely to accept indirect comparisons for claims of noninferiority, and G-BA clearly request ITC to be used only where it is not possible to perform head-to-head comparisons.

In summary, indirect treatment comparison methods are vital for establishing the treatment effect of a health technology against a comparator that is not included in the same study. However, all indirect treatment effect estimates are at risk of being impacted by confounding. The current PBAC Guidelines provide recommendations for the use and presentation of indirect comparisons that is consistent with international approaches.

Options: The use of indirect comparisons

1. *The use of indirect comparison methods should adhere to the proposed principles outlined above.*
2. *As the success of an indirect comparison is contingent upon the transitivity of the compared studies, require the presentation of a comparison of study characteristics, as well as how successful efforts for controlling for differences in characteristics are likely to be.*

Curation of control groups

In circumstances where a health technology has only single-arm data, a comparator arm must be sourced. In many cases, a comparator has previously been studied, and indirect comparison methods exist (such as MAIC and STC) that may reduce the impact of known confounders. These methods may be preferable to the use of a non-trial-based control group.

However, where there are no reliable published studies to source a control group, there are methods for creating a control group. Methods identified during the scoping search were:

- Intra-individual comparisons, where prior lines of treatment of study participants in the single arm study are used as a control.
- Generation of a control arm using post-progression survival from a study of a prior line of therapy.
- Generating an external control arm from RWD

For chronic diseases or slowly progressing diseases where disease management is the primary outcome of interest, a comparison of treatment outcomes in a single arm study with the prior line of therapy (i.e., before enrolment) may assist in estimating the benefit of a new health technology against a relevant standard of care. Such an

approach does, however, have considerable limitations and is unsuitable for estimating a treatment effect where OS is the outcome of interest.

The articles included in the scoping review describing the use of intra-individual comparisons provided very few examples of the use of this approach and noted that G-BA did not accept this approach to support HTA decisions on the basis of the methodological limitations. The use of before-and-after studies, whether prospectively designed or involving retrospective data collection, also have significant limitations, often relating to whether the standard of care and management of patients differs over time, whether there are losses to follow-up and whether the same patients are being measured before and after or are different.

Where OS is required, and a trial of a prior line of therapy is available, a control arm representing post-progression survival of the prior line of therapy may be derived from the progression-free or disease-free curves and the OS curve. This approach also has limitations. It has both the uncertainties associated with an unanchored indirect comparison as well as uncertainties associated with deriving the counterfactual OS based on post-progression survival (and the impact of delay between progression in a prior line and the initiation of the proposed health technology).

The use of RWD to generate external control arms may provide an option where randomised clinical trials are missing, and suitable control arm data are not published. The literature identifies early engagement with decision makers (regulatory and/or HTA agencies) as an important step, indicating a preference that the approaches are pre-specified. Due to the lower level of certainty driven by potential confounding and bias, and the non-transparent process of collecting and analysing data, methods involving RWD for the development of external controls should be strongly justified. Analyses involving multiple sources, or the application of multiple approaches, may be required to demonstrate the reliability of the results.

Despite the increase in the number of regulatory approvals based on single arm or uncontrolled studies, the use of external control arm studies are commonly rejected by regulatory and HTA agencies [627]. The FDA stated that the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low [628]. For this reason, the use of an external control study should be adequately justified, and may be more acceptable in rare diseases with unmet need, poor prognosis and large effect sizes [484], or as part of a coverage with evidence development arrangement.

Table 70 Advantages and limitations of different approaches for developing control arms

	Advantages	Limitations
Intra-individual comparisons	Comparisons are matched on disease and demographic characteristics. Comparator (standard of care) is likely to be relevant and contemporary. May be appropriate for chronic diseases where treatment switching occurs after	Collection of outcome data is retrospective. Diseases with rapid decline (e.g., some oncology indications), subsequent lines of therapy tend to have shorter durations of response, regardless of treatment efficacy. Comparisons of OS cannot be performed.

	loss of efficacy (where the main goal is disease management).	Comparison is not pre-specified and may be selectively applied (i.e., only used if favourable).
Historical control derived from post-progression survival of prior line of therapy	Can provide an estimate of incremental OS. Comparator patient population also derived from a clinical study setting, therefore likely to be more comparable than RWE (registries).	Transitivity issues associated with comparability of studies. Matching methods may be required. Requires methods to account for a delay in the initiation of subsequent therapies. If estimates are not adjusted, large delays between progression on a prior line of therapy to initiation of the health technology of interest may underestimate the incremental OS of the new treatment. Comparison is not pre-specified and may be selectively applied (i.e., only used if favourable).
Control studies from RWD or synthetic controls	Cohorts developed from RWD permit the comparison of single arm study data where randomisation is difficult and may be particularly helpful in the study of rare diseases. Synthetic cohorts can be generated from aggregate data, overcoming issues of privacy and unavailability of IPD.	The validation of methods for control arms developed from RWD is challenging and will be affected by data quality and the transitivity of the registry participant population with the study patient population. The findings are at risk of being confounded as a result of differences in patients, as well as definitions of outcomes, settings, clinical practice etc. More work is required to develop a framework for the robust collection and analysis of RWD.

IPD = individual patient data; OS = Overall survival; RWD = real world data; RWE = Real-world evidence.

Options: Use of external or intra-individual control groups

1. *The adoption of methods for the creation of control groups should adhere to the proposed principles outlined above.*
2. *Require justification of why an indirect comparison is not possible, or less reliable, than the proposed approach of creating a control group.*
3. *Require justification for the use of methods that are not prespecified in the study protocol of the proposed technology.*
4. *Require multiple approaches and/or multiple data sources, if possible, and a discussion of any inconsistencies in estimates.*

Nonrandomised evidence

HTA agencies are increasingly being required to consider nonrandomised studies, such as observational studies or nonrandomised clinical trials, but only NICE provided guidance on conducting specific data-analysis and NMA methods for combining data from randomised and nonrandomised studies.

Methodological guidance identified in the literature tended to be related to the conduct of the studies and did not cover in depth the evaluation or appraisal of such studies.

The literature noted that nonrandomised studies should only be used where it can be justified. In the context of HTA and for the purpose of treatment effect elicitation, justification should involve the inability to properly randomise patients to a comparative study. Most recommendations for the conduct of nonrandomised studies

were consistent with best practice for randomised studies, including pre-registration of protocols, engaging with regulators and HTA agencies in the planning phase, reporting data and methods transparently, assessing biases using a validated tool and describing and quantifying uncertainty. An additional step involves the identification of risk of bias / confounding prior to initiation of the study and to employ methods to minimise the risk.

Recommendations that were specifically addressed to HTA bodies included applying conditional reimbursement processes to ensure ongoing evidence after initial reimbursement, and to issue and enforce best practice guidance for the reporting of nonrandomised studies.

Even well conducted nonrandomised studies are unlikely to generate the level of certainty in the treatment effect that is possible with randomised studies, simply because randomisation allows for balance in unmeasured confounders between treatment arms (if the study is of decent size). Nonrandomised studies remain prone to limitations that may be difficult to identify and correct for.

Options: Use of nonrandomised studies

1. *The adoption of methods for the use of nonrandomised (observational) studies should adhere to the proposed principles outlined above.*
2. *The use of nonrandomised studies to estimate a treatment effect should be well justified, prospectively designed (preferably in collaboration with HTA or regulatory scientific advice) and registered, supported by multiple sensitivity analyses and transparently reported.*

Adjustments for treatment switching

In some cases, permitting patients to switch to the intervention arm following disease progression while receiving the comparative treatment may improve enrolment into a study, and may be more acceptable to ethics committees. However, if a patient relevant endpoint for the purposes of establishing value is OS (or an endpoint that occurs after the option to switch), HTA bodies may be interested in an estimate of the incremental OS had the switch not occurred. Although, it should be noted that as evaluations are done on an intention-to-treat basis that switching from the control arm to the intervention arm will likely reduce the magnitude of incremental benefit observed between trial arms and so is a conservative estimate.

Statistical adjustment for treatment switching may be less required in some other circumstances, such as to support a claim of noninferiority that may be adequately supported by a comparison of the intermediate outcomes. This approach may only be reasonable if the indirectly compared treatments are of the same class or have the same mechanism of action.

Current *PBAC Guidelines* provide a summary of the proposed methods and requirements for reporting.

Options: methods that adjust the treatment effect in the presence of treatment switching

1. *The adoption of methods for the use of nonrandomised (observational) studies should adhere to the proposed principles outlined above.*
2. *Require multiple methods to be reported to show consistency of the results. This may include alternative approaches (not only methods to adjust for treatment switching) such as translating intermediate endpoints unaffected by treatment switching into final outcomes.*
3. *Require a justification of the use of methods that are not pre-specified in the trial protocol of the key study for the proposed technology.*

Real-world evidence

Approximately half of the HTA jurisdictions investigated suggested that non-peer reviewed data could be incorporated into HTA evaluations for evaluating clinical effectiveness, but only the US ICER has produced a 'Policy on Inclusion of Grey Literature in Evidence Reviews' to guide the inclusion of non-peer reviewed evidence.

The scoping review identified many studies describing the use of RWD, with more than 20 articles presenting RWD or RWE as the main focus. Many more articles noted that the use of existing sources of RWD may be informative for reducing gaps in evidence, or recommend the ongoing collection of RWD to reduce uncertainty following provisional reimbursement.

Despite the considerable increase in references to the term "real-world evidence" over recent years, the use of RWE in HTA is not new. Disease registries, billing databases, utilisation data, epidemiological data, sources of costing and so forth have been used to justify treatment algorithms, the choice of comparator, the long-term safety of a medical product and parameterise economic and budget impact models. Nevertheless, less than half of the HTA jurisdictions investigated provided any guidance for its use for these purposes. However, despite the pervasive use of RWE for these purposes, HTA has been cautious regarding the use of RWE to inform the *treatment effect* of a technology under consideration. This is because it is well known that observational evidence is at a higher risk of bias and confounding than RCTs.

The other point to note for RWE is that the results of a medicine in clinical practice will likely be less beneficial than in a trial setting because trial populations are carefully selected to have fewer comorbidities and provide greater opportunities to respond to a treatment. As a consequence, trial evidence may be less applicable to 'real world' populations (external validity) but have much higher internal validity (the impact of the new medicine alone can be more reliably determined).

The focus of the commentary in this Review relates to the use of RWE to inform the effectiveness of health technologies.

Despite the increased interest in RWE in the literature, the use of RWE as the sole source of evidence for effectiveness does not appear to be commonly accepted across HTA bodies, and there is no indication that this position is changing for the appraisal of most health technologies. That HTA bodies are reluctant to consider RWE as the primary source of effectiveness evidence appears justified as key barriers reported in the literature are the often-poor quality of RWE and the lack of transparency in the generation of RWE. This is supported by a recurring recommendation across many included studies, which was to improve data collection methods.

Opportunities for the use of RWE in HTA are likely to be uncommon, but may include circumstances where randomised trial data are unable to be generated (such as for rare diseases), or to support a provisional HTA decision (e.g. coverage with evidence development).

The recent interest in RWE has resulted in several frameworks and guidance documents describing practices for its collection and evaluation. However, definitive guidance is undermined by a lack of a narrow or clear definition of RWE as it applies to HTA. Real-world evidence can be generated from a range of different data sources using a range of different methods and can be used to inform many steps in HTA reimbursement decision-making. Consequently, it is difficult to discuss broadly the opportunities and risks for the use of RWE in HTA. Akehurst et al (2023) conclude, "statements about how RWD should be used to produce credible RWE should not usually be made unless the precise question that is to be answered (and possibly the stage in appraisal at which it is posed) is specified" [490]. Prior to considering the implications for the use of RWE, it is important to define specific pairings of data and use cases. The literature calls for agreement around a definition [500] and taxonomy for RWE [490]. The proposed taxonomy would include the questions that are commonly addressed by RWE within HTA and the types of data sources and methodological techniques that may be used to address these questions.

In summary, HTA bodies remain cautious regarding the use of RWD to establish the effectiveness of a health technology, due to issues of data quality and transparency of the collection and analysis methods. Adopting RWE in circumstances where RCTs, or even anchored indirect comparisons, can be generated would currently result in a considerable loss of decision-making confidence and in possible suboptimal outcomes for patients. No identified study reported benefits of RWE that included increasing transparency or reducing the time to access for patients, although in circumstances where there are no other options for effectiveness data, improved access may be self-evident.

The use of RWE is not well established enough to recommend its adoption for the estimate of treatment effectiveness outside of exceptional circumstances. These circumstances still need to be clearly defined and reflect cases where the use of RWE is likely to be beneficial to patients and payers. It is likely that such use cases would include:

- The assessment of rare diseases or conditions
- The generation of control arms for rare diseases or conditions
- The collection of data to confirm effectiveness claims through coverage with evidence development

Options: The use of RWD and RWE in HTA

1. *The adoption of methods for the use of real world data and real world evidence should adhere to the proposed principles outlined above.*
2. *Greater guidance for the use of RWD and RWE in HTA is required. As well as a curated list of methods that may be used to generate RWE, guidance should consider what data sources would be acceptable for particular purposes (e.g. costs, utilities, treatment effect). Guidance should also adopt a terminology that defines different sources of RWD more precisely than the umbrella term of "RWD". Specific guidance is required regarding the assessment of the quality of the data source, and it may be an option to require a minimum standard of data quality prior to use in HTA.*
3. *RWE should not be acceptable to use for the purpose of determining treatment effectiveness of a technology unless the following conditions are met, or there is a strong justification that they cannot be met:*
    a. *The technology is for use in a population with a high unmet clinical need*
    b. *Higher quality evidence cannot be generated, or will not be generated in a timely fashion*
    c. *Multiple sources of RWE are presented (including both methods of generating RWE from a source, and multiple RWD sources)*
    d. *The use of RWE is prespecified in the study protocol for the proposed technology*

Surrogate endpoints

Little information about technologies with limited data on long term outcomes or with a rapidly changing evidence base was available from any jurisdiction, except when the technology was an orphan drug for a rare disease. Two Canadian jurisdictions are proposing time-limited reimbursement recommendations for emerging technologies with continually emerging evidence, which would be contingent on a future reassessment of additional evidence that addresses the uncertainties with the comparative clinical benefit and cost-effectiveness of the technology.

Methods for establishing the association between surrogate endpoints and final patient-relevant outcomes are similar across HTA agencies. It should be noted, however, that in many cases, surrogates that have been robustly validated are those that are the least likely to be required in HTA. It is often disruptive technologies or

technologies for rare diseases that may most benefit from the use of surrogates, yet surrogates in these contexts have the least evidence supporting their application.

Methods for validating a surrogate endpoint are well established and are described in the current *PBAC Guidelines*.

Benefits associated with increasing the use of surrogate endpoints in HTA:

- Permits the estimation of the value of a technology that has received regulatory approval based on surrogate endpoints for the purpose of a provisional reimbursement decision.
- Permits the estimation of the value of a technology that is unlikely to generate evidence that includes final outcomes.
- Supports the estimate of the treatment effect for technologies that have high rates of treatment switching, thus confounding the trial estimate of the final outcome.
- Faster access to new health technologies.

Risks associated with increasing the use of surrogate endpoints in HTA:

- The use of surrogate endpoints in HTA decision-making is not supported by robust methods of translation or methods for mitigating risk associated with uncertainty of the relationship as it is applied in the submission.
- Despite the application of robust methods to translate surrogate endpoints to final outcomes, future evidence invalidates or alters the relationship between the surrogate endpoint and the final outcome.
- The treatment effect on surrogate endpoints is more likely to be favourable than the treatment effect on final outcomes, and treatment effects tend to be larger for surrogate endpoints than for final outcomes [629, 630]. Therefore, there is a risk that the translation of surrogate endpoints to final outcomes may overestimate the treatment effect of the proposed technology.
- Surrogate endpoints for rare diseases, small populations or when using special technologies (ATMPs) may not have adequate supporting evidence to robustly translate the surrogate endpoint to the final outcome.
- An established surrogate to final outcome relationship is applied outside of the circumstances in which it was validated.

Options for methods relating to the use of surrogate endpoints

1. *The adoption of methods for the use of surrogate endpoints in HTA should adhere to the proposed principles outlined above.*
2. *Guidance for the use of surrogate endpoints in HTA should include circumstances where surrogates would be acceptable (and may include a list of previously accepted surrogate endpoints paired with use cases). Guidance should also revisit*

methods required to validate surrogates to ensure they are achievable by industry, and include methods for describing the uncertainty in the use of surrogate endpoints, particularly where surrogate relationships are used in combination with other methods (such as indirect comparisons or model extrapolation) where uncertainty may be substantially increased.

3. *Guidance for the evaluation of evidence using surrogate endpoints is required, and should include methods for identifying the use of surrogates in submissions (as surrogate relationships can be implicit in economic models but not adequately presented for clinical evaluation).*

VALUE FRAMEWORKS

The scoping review identified many articles discussing value frameworks used in HTA. In general, HTA bodies employ value frameworks that encompass elements broader than clinical effectiveness, cost-effectiveness and budget impact.

In some cases, value frameworks that are specific to indications (such as rare diseases) or treatments (ATMPs) have been proposed. Several included studies provided clear justification for certain diseases or technologies having impacts that are not easily captured using narrow value frameworks. However, it was not well justified that broader value frameworks would not be equally applicable to the evaluation of all technologies.

One strong recommendation within the literature was the adoption of an explicit value framework. The term explicit is intended to mean that the value elements the committee considers, how they consider them, and what impact the value elements have on decision-making are known.

There are clear benefits of adopting a single generic value framework that allows the committee to consistently consider value elements across all technologies. Some of these benefits might be: improving committee familiarity with a single, broader value framework which promotes consistency and predictability of decision-making; avoiding the need to create or consider a new value framework for multiple diseases or technologies; avoiding eligibility criteria for the use of particular value frameworks; and ability of an applicant and patients to address a familiar framework. There may be some trade-offs if a broad, but generic value framework is used, such as a loss of sensitivity of the framework (ability of the framework to capture the full value of a health technology). However, a broad value framework that permits other relevant factors to be discussed will likely provide the decision-making committee sufficient flexibility to incorporate additional value elements.

The Pharmaceutical Benefits Advisory Committee provides some insight into the value framework upon which it bases its recommendations to Government. This framework is outlined by the stated factors that influence committee decision-making, and include comparative effectiveness and safety, cost-effectiveness, financial implications, equity,

clinical need, severity of the condition and public health issues. While these value elements are explicitly stated, how the committee considers these elements and the impact they may have on decision-making is not transparent. Furthermore, it is unclear how the committee informs deliberations regarding some of the value elements. The current *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee* (version 5.0) does not specifically request information from sponsors that would permit a consistent application of a broader value framework [187]. Therefore, data gathering for various value elements may be limited.

The benefit of an explicit value framework is that stakeholders (applicants, HTA agencies, patient groups, committee members) will seek to consider the value domains for each technology assessment. The explicit value framework would then be addressed by applicants in a consistent way and may be a useful tool for patient or public submissions to target areas of value that might otherwise be poorly understood by the committees.

The literature discussed three key types of value frameworks.

- Quantitative MCDA
- MCDA with decision-rules
- Qualitative value framework (also referred to as qualitative MCDA)

MCDA has been defined variously over the years, and more recent definitions appear to be exceedingly broad. It may be preferable to define processes of considering a value framework more precisely than describing all processes that consider more than one parameter an "MCDA". Historically, the term MCDA related to models that aggregated scores across multiple value elements into a single score.

For this report, 'qualitative MCDA' is simply referred to as a value framework, 'quantitative MCDA' is referred to as MCDA, and 'MCDA with decision-rules' is referred to as value-based decision-rules.

MCDA

Quantitative MCDA applies a score to each value element for decision-making, which is then synthesised using pre-determined weights and an overall score is generated.

Although there were many articles stating that the use of quantitative MCDA enhances transparency and predictability of decision-making, there were several articles that discussed the limitations of quantitative MCDA. Many of the purported benefits of MCDA remain untested, and no studies were identified that reported on the impact of MCDA on the quality of decision-making. We found no evidence that currently, any HTA agency routinely employs quantitative MCDA.

The applicability of quantitative MCDA methods to the Australian context is difficult to assess. Typically, the result of an MCDA is intended to provide a decision based on the domains included in the MCDA, and the pre-determined weightings for each of the

domains. While the consideration of value domains beyond effectiveness, cost-effectiveness and budget impact is important in HTA, it is unclear whether a quantified approach would necessarily improve HTA decision-making or the HTA process in Australia.

Where an MCDA requires additional time to develop, and additional evaluation time to validate the parameters included in the MCDA, it is possible that such a method would slow the HTA process. Furthermore, where an MCDA result is sensitive to key parameters, the quality and applicability of the data are likely to be scrutinised and may result in tensions between the sponsor providing the data and decision-makers. Currently, committees and sponsors may have different views regarding the most plausible parameters in an economic evaluation, and these tensions may increase to other parameters should a quantitative MCDA model be implemented.

Decision-rules

NICE have recently updated their value-based pricing approach, which incorporates "decision modifiers". The current decision modifiers are those factor that have not been included in the estimate of the QALY and include disease severity (measured by absolute or relative QALY shortfall) and size of benefit for highly specialised technologies (measured by absolute QALY gain). Some studies have referred to this approach as MCDA with decision rules. The committee also includes structured decision making for uncaptured benefits and non-health factors.

Value frameworks

The method employed by the US ICER presents an interesting approach to explicitly considering factors in a broader value framework. The US ICER has created a simple value framework that is considered alongside clinical effectiveness, cost-effectiveness and budget impact. The components of the framework are:

- Contextual considerations:
    - Clinical need
    - Severity of disease (and lifetime impact on patient)
- Other benefits and disadvantages
    - Broader impact on patient (in terms of major life goals)
    - Impact on caregivers (QoL and major life goals)
    - Complexity of treatment
    - Health inequities

It is noteworthy that the contextual considerations included in the US ICER's value framework are similar to those considered by NICE in it's decision rules.

During deliberations, the committee is requested to consider and rate the additional broad value elements that may impact the overall long-term value of the treatment. The committee then considers the impact of these additional value elements on the target ICER range, with more favourable ratings of value elements resulting in a decision of cost-effectiveness toward the top of the ICER range.

Although the committee may have a more publicly understood target QALY threshold (or range), the benefits of the application of this approach may be realised in the absence of an explicit threshold. These are:

- Formalising the approach to considering additional factors as part of committee deliberations, which may elevate the importance of some values held by patients or by society that are often not captured in traditional assessments.
- Ensuring that the committee engages with other relevant factors in a systematic way (such as using a list of factors that committee members may score using a Likert scale). It also allows the committee to reflect and learn how other relevant factors influence their decision-making. Currently, the approach to considering other relevant factors is not explicit and it is unclear whether committee members consistently address factors for each appraisal. Such a process is likely to require a period of learning, however may culminate in a more rigorous consideration of other relevant factors in future deliberations.
- Permitting the sponsor to provide evidence of impacts on other relevant factors. This is facilitated by the development of a short list of other relevant factors (beyond clinical effectiveness, cost-effectiveness and budget impact), and a request to provide information in a submission.
- A list of other relevant factors may also provide guidance to patients or other stakeholders on what to provide input during the consultation process.

A published summary of the committee's deliberations, possibly addressing each of the included value elements, will provide transparency and reassurance that the committee is cognizant of the impacts of a technology or a disease that are beyond health.

Options: The use of value frameworks

1. *To increase the transparency of committee decision-making regarding value elements beyond clinical effectiveness, cost-effectiveness and financial impact, it is an option that the committee adopt an explicit value framework. This may also provide greater confidence that the committee is taking a patient centric approach, and considering factors that are of value to both patients and society. While adopting a quantitative MCDA approach may be an option, the benefits and resource requirements of such an option remain uncertain. The adoption of a qualitative value framework would include:*
    - *Generation of an explicit value framework consisting of broader elements, designed to reflect patient and societal values but retain flexibility should the committee wish to incorporate additional value elements. The development*

of a value framework for Australian HTA may leverage existing frameworks and should be agreed upon through consultation with relevant patient groups or consumer representatives and clinical experts.

- *Documentation regarding how the framework will be considered during committee deliberations.*
- *Guidance explaining how:*
    - *Sponsors could provide data to respond to additional value domains*
    - *Patients or citizens could provide submissions to respond to additional value domains*
- *Consideration of how the committee deliberations as they relate to the additional value elements will be made public.*

The development of a value framework that is acceptable to consumers, experts and the committee would require resources and consultation. However, once developed, the application of a value framework in Australian HTA would not likely require additional resources. Data for informing the value framework may be provided in a submission to a decision-making committee and would be evaluated. The process of evaluation would relate to establishing the reliability of the data (preferred methods for considering expert data are described in Appendix 1 of the PBAC Guidelines). Data may also be gathered from submissions from patients, or patient groups, to be considered by the committees. If patients are instructed to address the components of the value framework, this may assist in the compilation of patient input for presentation at committee meetings.

The use of the value framework by the committee during deliberation may add a small amount of time to the deliberation process, particularly if the committee are provided with the opportunity to individually score the value framework and the aggregated results are presented back to the committee for appraisal.

A broad and non-technology specific value framework has the benefit of being standardised across all HTAs, and, if generated appropriately, would not limit the factors that the committee considers. To maintain flexibility in the decision-making process, the broad aims of the consideration of the value framework could be described in similar terms as has been done in the US ICER's recent reforms. See Figure 33.

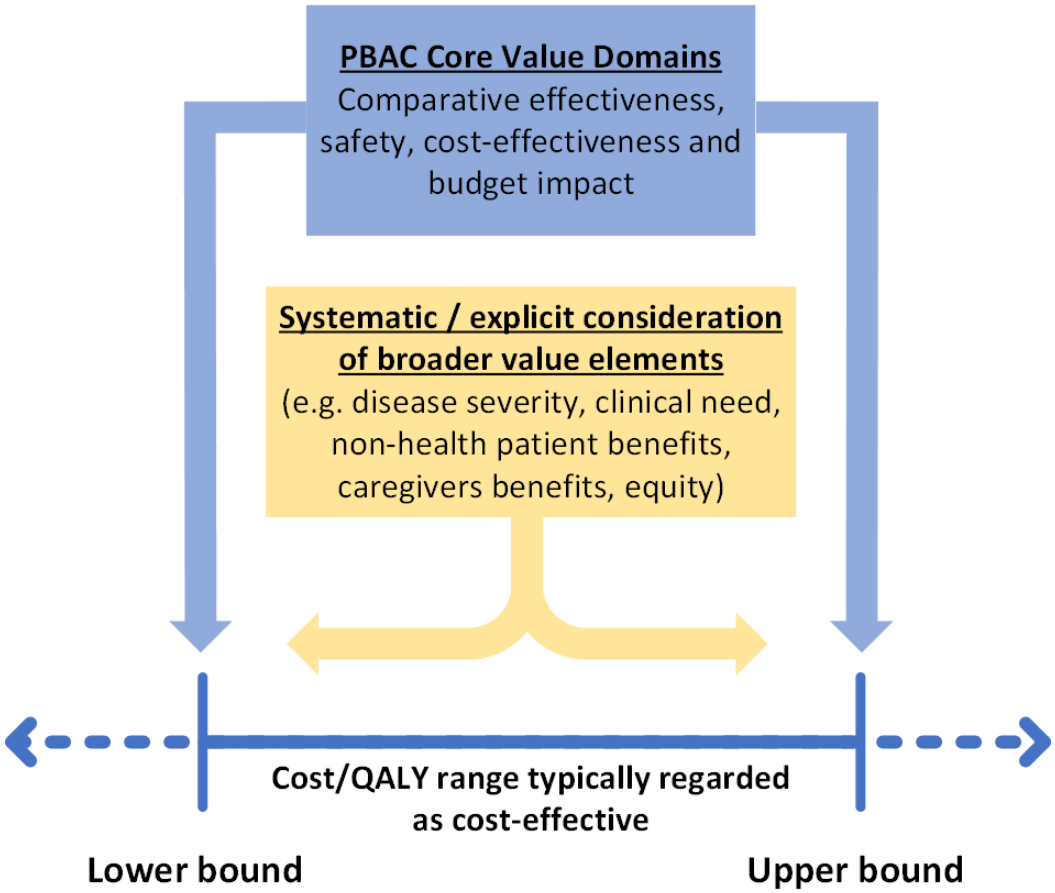

Figure 33 Conceptual implementation of additional value domains during committee deliberations of value

Adapted from page 34 of US ICER 2020-2023 Value Assessment Framework [32]

QALY = quality-adjusted life years.

EQUITY

Of the seven jurisdictions that considered equity issues during the decision-making process, only four jurisdictions, including Australia (PBAC and MSAC) provided guidance as to how to provide this information.

Equity should continue to be considered by appraisal committees mostly in a deliberative fashion in view of methodological limitations in handling equity quantitatively. However, Australia should investigate the potential role and merit of DCEA as something that could enhance deliberation. Australia should attend to how equity considerations might count against, and not be always in favour of, a technology under review.

A checklist should be created to assist HTA decision makers to integrate equity considerations into their deliberations in a more comprehensive and systematic way. The checklist should build on published research [377, 557] but also be informed by a concerted exercise in public engagement, as occurred in South Africa [95]. This checklist

could essentially be rolled into, or form part of, the explicit value framework mentioned above.

The potential merit of using "efficiency frontiers" to inform price negotiation where multiple therapeutic options are available and comparison across conditions or disease areas is not sought, should be considered (this might be the case with some very rare diseases).

STAKEHOLDER/PATIENT ENGAGEMENT

Increasingly in HTA there is a focus on patient experiences and perspectives, i.e., patients' own views of what matters to them in relation to their medical condition and its treatment. It is considered increasingly important in decision-making when considering the listing of medical products for reimbursement. Patient perspectives should inform the outcomes that are studied in primary or pre-market research (e.g., by industry and academia). HTA bodies could explicitly flag their willingness and interest in receiving evidence submissions that include (even centrally) such research, e.g., patient reported outcomes (PRO) research and patient preference elicitation studies. HTA bodies should clearly signal how such studies would factor into decision making. Greater clarity is needed on how patient preference studies ought to be conducted and on how they would be used in decision making.

Population, Intervention, Comparator, Outcome (PICO) selection could include greater patient engagement, e.g., to focus on the outcomes that matter to patients. However, if patient engagement identifies some outcomes as important, but published studies do not focus on these, then this could mean that the evidence base to inform the funding decision would be limited, even if well aimed at what matters to patients. Nonetheless, this would flag the need for this evidence. It is very important that Australian HTA processes are clear on how information from patient engagement is, and will be, used, namely to increase patient confidence and to guide patients on the information that is helpful to provide. In Australia, the MSAC Guidelines 290 provide guidance on how to incorporate consumer evidence into an HTA evaluation. The PBAC Guidelines provide less relevant guidance on the incorporation of consumer evidence, however the PBAC procedure guidance does explain how consumer evidence can be submitted and how it will be considered185.

Option:

1. *Consideration should be given to supplementing the Australian PBAC Guidelines to provide guidance for the inclusion of consumer evidence to help inform decision-making that extends on the guidance provided in the PBAC procedure guidance. Such guidance should be consistent with reforms adopted in response to the HTA review, particularly in terms of the proposed value framework. A broader and explicit value framework may act as an appropriate basis for guiding*

consumer submissions to elements that will be most influential during committee deliberations.

Australia already appears to have an internal government team dedicated to patient engagement, e.g., running a mentoring programme for patient representatives on committees. This is the Consumer Evidence and Engagement Unit (CEEU) within the Department of Health and Aged Care. Australia also has a HTA Consumer Consultative Committee (CCC), comprised of each consumer member from PBAC, MSAC and PLAC and their related sub-committees631. This committee provides strategic advice and support on patient involvement, collaborating with the CEEU, whose work should be made clearer to the public and could be extended to conducting or contracting (e.g., to HTA agencies) proactive outreach activities whereby small-scale qualitative research is conducted (e.g., six interviews with patients or representatives and a fairly straightforward thematic analysis of this data over the course of six weeks). This routinely occurs in Ontario, Canada, where the reports serve as additional inputs to funding deliberations alongside analyses of safety, effectiveness, cost-effectiveness, and so on. Ontario has a formal "public and patient involvement framework" that features substantive theory and methodological detail632. However, there is some level of disagreement and uncertainty about the proper role and actual impact of patient engagement, so the role should be clarified (acknowledging conflicts between epistemic traditions) and quality and impact should be monitored, building on existing frameworks (e.g.,HTAi Values and standards for patient involvement in HTA 565, 134,633, 634. A relevant impact is increased confidence in patients in fair decision making and increased confidence of committee members in making well-informed and good decisions. Networks and strategies would need to be in place to facilitate timely patient recruitment. Relevant capacity building (e.g., in government, patient organisations or contracted HTA agencies) should also occur to facilitate recruitment and data collection and analysis. Appropriate resourcing of patient groups would also assist them to provide information needed for HTA evaluation and appraisal of medicines and reduce scope for undue industry influence on patient groups (real or perceived). Expert opinion suggests that, in resourcing patient groups, due consideration would need to be given to appropriate skills as well as finances (e.g., training and capacity building).

Much of the above (e.g., resourcing patient engagement and being very clear on how patient inputs will and have been used in decision making) would serve to promote a culture that is actively and explicitly inclusive of patient perspectives.

Australia should investigate the potential role and value of greater public (as distinct from patient) engagement in HTA. Invitations for public comment on assessment reports mostly occasion industry comments on evaluation methods. Conducting decision making meetings in public would improve transparency but not necessarily help to guide decisions according to public values and preferences (especially around the opportunity cost of funding a new medicine). Enhanced public engagement should begin as part of

creating the checklist or value framework to assist HTA decision makers to integrate equity considerations.

In five jurisdictions, the approach taken to obtaining evidence from patients or patient organisations differs from that in Australia and the other nine jurisdictions that incorporated consumer/patient evidence. In three jurisdictions (Canada, CADTH; Wales, AWTTC; Singapore, ACE) the input is coordinated by a dedicated patient engagement team, and one jurisdiction (Belgium, KCE) provided methodology for performing qualitative research to collect patient relevant data and experiences for inclusion in the HTA. Expert opinion suggests that patient engagement units exist in many HTA bodies, and that Denmark also provides guidance on qualitative research and Scotland on rapid qualitative evidence synthesis.

OTHER METHODS IDENTIFIED

Evaluating codependent technologies

Eight jurisdictions considered methods for the evaluation of codependent technologies, as distinct from the pathways identified in Paper 1. Three jurisdictions, including Australia (PBAC and MSAC) required a combined submission that encapsulates the safety, effectiveness and cost-effectiveness of the test and medicine.

Orphan drugs, rare diseases and ATMPs

Literature related to specific methods applied to the HTA for orphan drugs and rare diseases largely related to addressing evidence deficiencies and adopting broader value elements in decision-making. Methods relating to the assessment of nonrandomised evidence, surrogate endpoints and value frameworks are discussed in preceding sections.

Many studies discussed methods for the assessment of ATMPs. In most cases, these methods related to evidence deficiencies and adopting broader value elements in decision-making. These methods are discussed in preceding sections. Of note, much of the discussion relating to broader value frameworks appeared unrelated to the nature of the technology, and instead related to the population in which the technology is proposed to be used (i.e., rare or severe diseases).

A recurring theme in the literature discussing methodology for the assessment of ATMPs was the lack of methods to address evidence deficiencies, and the recommendation to adopt alternative reimbursement methods to mitigate the risk of large, upfront costs to payers.

Options for HTA methods applied to orphan drugs, treatments for rare diseases and ATMPs

1. *Consider the additional value elements related to disease severity and unmet need that may be relevant for rare diseases and ATMPs.*

2. *For diseases with unmet need and where sufficient evidence to establish adequate certainty of the magnitude of benefit cannot be generated prior to deliberation, consider provisional listing options.*
3. *Mandate the use of well-designed data collection to address evidence uncertainties for technologies given provisional approval that require continued evidence generation.*
    a. *Engage with and invest in existing registries where possible and if fit for purpose*
    b. *Invest in new data collection processes*
    c. *Ensure the Government retains access and the ability to utilise data collections for the assessment of current and future treatments*

Histology-independent treatments

The challenges of the evaluation of histology-independent treatments relate primarily to the evidentiary limitations of basket trials for estimating the benefit of a treatment across multiple cancer histologies. These limitations include small cohort sizes, lack of comparators, lack of external control data delineated by biomarker status, difficulty in translating intermediate outcomes (response rates) into patient relevant endpoints typically used by HTA bodies, uncertainty regarding the prognostic implications of the biomarker, and uncertainty in the uptake of testing and treatment. Methods for overcoming the challenges associated with basket trials are required due to the recent acceptance by regulators of histology independent treatments based on basket trials. However, no methods were identified that addressed the challenge of assessing histology-independent treatments. One study reported that the requirements of the French National Authority for Health (HAS) for the evaluation of histology-independent treatments did not markedly differ from traditional treatments.

An unpublished guidance document from AHTA, commissioned by the Department of Health and Aged Care, proposed that an exemplar approach could reduce the evidentiary burden of generating comparative evidence for each histology type [635]. This document is yet to be considered by the PBAC for inclusion as an Appendix to the *PBAC Guidelines*.

Options: consideration of histology-independent treatments:

- *Require adequate evidence to evaluate individual histologies. This may be possible for some common cancer histologies but may delay access for those with rarer cancers. The evidence may not be available for many small histology groups.*
- *For less common biomarker / histology pairs, assess the treatment as though it were a rare disease. If the condition has an unmet need, permit a provisional listing in combination with ongoing evidence generation. This approach will require additional resources.*

- *Create groups of histologies with similar characteristics and assess only representative histologies as a proxy (exemplar) for the group. Permit the aggregation of benefits and costs across all histology groups so that cost-effectiveness can be averaged over a number of cost-effective and less cost-effective histology groups. This will also have the benefit of a single price for a treatment across multiple target histologies.*

Antimicrobials and vaccines

Studies reporting on methods for the assessment of antimicrobials and vaccines tended to discuss the insufficiency of individual patient focused value frameworks for capturing value, and the challenges with current mechanisms of payment which are typically linked to sales.

Value frameworks proposed for antimicrobials included:

- the benefits and costs associated with the treatment of an individual
- the benefits and cost-savings associated with the reduction in the transmission of the disease
- the added value associated with the avoidance of antimicrobial resistance.

In addition, the value frameworks for vaccines included:

- Comprehensive cost-offsets within the health care system
- Impact on transmission and health of the unvaccinated population
- Prevention of antimicrobial resistance
- Productivity and macroeconomic effects

It should be noted that a reduction in antimicrobial resistance is not likely to occur unless many jurisdictions adopt the use of narrow spectrum antibiotics, as antimicrobial resistant bacteria can spread between countries.

The US ICER's value framework, as discussed in 0, partly captures the additional value elements for antimicrobials and vaccines. However, there may be considerable value associated with population-based impacts, such as the impact of transmission, herd immunity and the development of antimicrobial resistance, that are not explicitly included in this framework, suggesting that the framework might need amending for these types of technologies, should it be adopted.

One goal of antimicrobial development is to create very narrow or targeted antibiotics. Antimicrobials that precisely target specific bacteria are less likely to result in the development of antibiotic resistance. However, narrow spectrum antibiotics are likely to be used considerably less than broader spectrum antibiotics, and therefore the return on investment for sponsors is lower, creating a disincentive for their development. Payment methods that partially or wholly delink the payment method for vaccines from sales volumes have been trialled in Sweden and the UK. In both of these

cases, certainty of supply was part of the negotiation of the fee. In the UK, the derivation of value to support the subscription fee was not without challenges.

Options: evaluation of antimicrobials and vaccines

- *Incorporate additional value elements in the value framework considered by the committee. These value elements should incorporate the benefits associated with reduction in disease transmission, and reduction in the risk of antimicrobial resistance.*
- *Consider alternative payment methods that delink payments from sales volume.*
- *Incorporate agreements for guarantee of supply into payment mechanisms.*
- *Ensure that decision-making aligns with global strategies to address antimicrobial resistance.*

Precision medicine and genomic profiling

Precision medicines (treatments targeted at the treatment of biomarkers) are increasingly common. Current methods in Australia require that targeted treatments are assessed in parallel with the tests required to identify the targetable biomarker (codependent technology framework). This approach is partly to assess the validity of the test, and partly to account for the cost of testing to identify a patient with a targetable biomarker. However, testing methods are evolving such that a single test may be used for multiple treatments. As testing becomes more comprehensive (such as genomic profiling), linking the cost of a test to a single medicine may no longer be possible.

New testing methods may also provide considerable information beyond simply targeting a treatment to a biomarker, including providing prognosis or value of knowing information.

CONCLUSIONS

Health technology assessment is an established process in Australia and in many countries globally for evaluating the value of health technologies. In recent years, stakeholders have expressed concern about the speed of access to new health technologies in Australia, and in response, the Australian Government sought to undertake a broad review of the policies, processes and methods used in HTA in Australia (HTA Review).

Adelaide Health Technology Assessment (AHTA) authored four of the scoping review papers used to inform the HTA Review Options Paper. These papers examined: market approval, funding and assessment pathways; horizon scanning and early assessment; determination of population, intervention, comparator and outcomes for assessment; and, (clinical / epidemiological) methods for use in HTA.

The Papers (referred to as Paper 1 through 4 in this report) compared the characteristics of HTA as applied internationally with the Australian setting, and presented new methods or evidence that may be relevant to inform changes to the Australian system.

The findings of these papers, and the options for change proposed by AHTA, helped to inform the HTA Review Options Paper, which was published for consultation in January 2024.

As of March 2024, the outcomes of the HTA review are pending.

APPENDIX 1

The scoping review search terms and sources of information are provided below.

Bibliographic Search 1: Paper 1, Paper 2, Paper 3 and Paper 4

PubMed Search

Table 71 PubMed Search Terms (10th May 2023)

	Search terms	Hits
#1	"guid*"[Title/Abstract] OR "manual"[Title/Abstract] OR "recommend*"[Title/Abstract] OR "framework*"[Title/Abstract] OR "method*"[Title/Abstract] OR "best practice"[Title/Abstract] OR "reform*"[Title/Abstract] OR "process*"[Title/Abstract] OR "pathway*"[Title/Abstract]	12,018,760
#2	("Guidelines as Topic"[MeSH]) NOT "Practice Guidelines as Topic"[MeSH]	45,222
#3	"methods"[Subheading] OR "Methods"[MeSH]	4,876,630
#4	"Technology Assessment, Biomedical/methods"[MeSH] OR "Insurance, Health, Reimbursement"[MeSH]	49,201
#5	"Health Technology Assessment"[Title/Abstract] OR HTA[Title/Abstract] OR "health technology"[Title:~2]	11,144
#6	(#1 OR #2 OR #3) AND (#4 OR #5)	27,049
#7	#6 AND ((2018/1/1:3000/12/12[pdat]) AND (English[Filter]))	5,870

Embase search

Table 72 Embase Search Terms (10th May 2023)

	Search terms	Hits
1	guid*.ab,ti.	1,540,533
2	manual.ab,ti.	167,301
3	recommend*.ab,ti.	1,208,532
4	framework*.ab,ti.	432,810
5	method*.ab,ti.	12,161,897
6	best practice.ab,ti.	29,523
7	reform*.ab,ti.	74,306
8	process*.ab,ti.	3,300,422
9	pathway*.ab,ti.	1,808,518
10	practice guideline/	551,492
11	exp biomedical technology assessment/	17,099
12	HTA.ab,ti.	8,936
13	health technology.ab,ti.	12,258
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	16,646,759
15	14 not 10	16,256,369
16	11 or 12 or 13	28,572
17	15 and 16	16,505
18	limit 17 to (english language and yr="2018 -Current")	6,340

Bibliographic Search 2: Paper 2 (Horizon Scanning)

PubMed Search

Table 73 PubMed Search Terms (15 May 2023)

	Search terms	Hits
#1	"horizon scan*"[Title/Abstract] OR "environment scan*"[Title/Abstract] OR "early dialogue*"[Title/Abstract] OR "early awareness"[Title/Abstract] OR ("Early value"[Title/Abstract] AND "assess*"[Title/Abstract]) OR "Diffusion of Innovation"[Mesh] OR ("Technology Assessment, Biomedical"[Mesh] AND "early"[Title/Abstract])	22667
#2	"pharmaceutical"[Title/Abstract] OR "drug"[Title/Abstract] OR "vaccine"[Title/Abstract] OR "test"[Title/Abstract] OR "diagnostic*"[Title/Abstract] OR "gene therapy"[Title/Abstract] OR "cell therapy"[Title/Abstract]	4350465
#3	#1 AND #2	2091
#4	#3 AND ((2000/1/1:3000/12/12[pdat]) AND (english[Filter]))	1778

Embase Search

Table 74 Embase Search Terms (15 May 2023)

	Search terms	Hits
#1	"horizon scan*" ab,ti OR "environment scan*" ab,ti OR "early dialogue" ab,ti OR "early awareness" ab,ti	912
#2	"early value" ab,ti AND "assess*" ab,ti	8
#3	diffusion of innovation.mp. or exp "diffusion of innovation"/	941
#4	exp health technology assessment/ or exp biomedical technology assessment/ or health technology assess*.mp AND early ab,ti	1515
#5	#1 OR #2 OR #3 OR #4	3272
#6	#5 2000:2023 (sa year)	3108

HTA database search

The INAHTA HTA database was searched, in addition to the websites of the INAHTA HTA agencies shown in Table 76, to search for guidance documents.

Other Sources of information

Table 75 Non-bibliographic database sources of information for the scoping review

Source	Target Information	Website
HTA database	Paper 1: Agency methods documents (for general HTA methods and HTA methods for specific technologies) Agency guidelines and policy documents	https://database.inahta.org/
INAHTA member agencies[a] that are not on the OECD list of LMIC	Paper 1, Paper2, Paper 3 and Paper 4: Agency methods, guidelines and policy documents	Member websites
Key international jurisdictions[b]	Paper 1, Paper 3 and Paper 4: Broad search for HTA-related methods, guidelines and policy documents for the jurisdiction (including Government or decision-making body websites). This was particularly important for guidance on vaccines, which was not comprehensively covered by INAHTA agencies or the bibliographic database search. Paper 2: Search for horizon scanning and early assessment-related methods, guidelines and policy documents for the	Various

	jurisdiction (including Government or decision-making body websites)	
Pearling and snowballing	Paper 1 and Paper 4: Citations of relevant articles will be selectively searched to identify additional relevant information. Paper 2: Early included studies were searched for backwards and forwards citations using spidercite; references that could not be automatically searched were manually searched using SCOPUS Paper 3: Citations of relevant articles were searched to identify additional relevant information using SpiderCite. In addition, SpiderCite was used to identify articles which had cited the articles of interest.	https://sr-accelerator.com/#/

a See Table 76

b United Kingdom; Canada; European Union; Taiwan; Korea; Netherlands; Germany; France; and the United States of America

Abbreviations: HTA = health technology assessment; INAHTA = International Network of Agencies for Health Technology Assessment; LMIC = low- and middle-income countries; N/A = not applicable; OECD = Organisation for Economic Co-operation and Development.

APPENDIX 2

INAHTA member agencies

Table 76 Names of INAHTA member agencies that are not included in the OECD list of LMIC

HTA Agency Abbreviation	HTA Agency Name	Country of Agency
ACE	Agency for Care Effectiveness	SINGAPORE
AETS	Agencia de Evaluación de Tecnologias Sanitarias	SPAIN
AETSA	Andalusian Agency for Health Technology Assessment	SPAIN
Agenas	The Agency for Regional Healthcare	ITALY
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	AUSTRALIA
AIHTA	Austrian Institute for Health Technology Assessment	AUSTRIA
AOTMiT	Agency for Health Technology Assessment and Tariff System	POLAND
AP-HP	Assistance publique- Hopitaux de Paris	FRANCE
AQuAS	Agència de Qualitat i Avaluació Sanitàries de Catalunya	SPAIN
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical	AUSTRALIA
AVALIA-T	Galician Agency for Health Technology Assessment	SPAIN
C2H	Center For Outcomes Research And Economic Evaluation For Health	JAPAN
CADTH	Canadian Agency for Drugs and Technologies in Health	CANADA
CDE	Center for Drug Evaluation	Taiwan, REPUBLIC OF CHINA
DEFACTUM	Social & Health Services and Labour Market	DENMARK
FinCCHTA	Finnish Coordinating Center for Health Technology Assessment	FINLAND
G-BA	The Federal Joint Committee (Gemeinsamer Bundesausschuss)	GERMANY
GOeG	Gesunheit Österreich GmbH	AUSTRIA
HAD-Uruguay	Health Assessment Division, Ministry of Public Health	URUGUAY
HAS	Haute Autorité de Santé	FRANCE
HIQA	Health Information and Quality Authority	IRELAND
HIS	Healthcare Improvement Scotland	UNITED KINGDOM
HTW	Health Technology Wales	UNITED KINGDOM
IACS	Health Sciences Institute in Aragon	SPAIN
IHE	Institute of Health Economics	CANADA
INESSS	Institut national d'excellence en santé et en services sociaux	CANADA
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	GERMANY
KCE	Belgian Health Care Knowledge Centre	BELGIUM
NECA	National Evidence-based healthcare Collaborating Agency	KOREA
NICE	National Institute for Health and Care Excellence	UNITED KINGDOM
NIHR	National Institute for Health Research	UNITED KINGDOM
NIPH	Norwegian Institute of Public Health	NORWAY
OH	Ontario Health	CANADA
OSTEBA	Basque Office for Health Technology Assessment	SPAIN
RER	Regione Emilia-Romagna	ITALY

SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services	SWEDEN
SFOPH	Swiss Federal Office of Public Health	SWITZERLAND
TRC	Behandlingsrådet(The treatment council)	DENMARK
UVT	HTA Unit in A. Gemelli Teaching Hospital	ITALY
ZIN	Zorginstituut Nederland	THE NETHERLANDS
ZonMw	The Netherlands Organisation for Health Research and Development	THE NETHERLANDS

Abbreviations: INAHTA = International Network of Agencies for Health Technology Assessment; LMIC = Low and Middle Income Countries; OECD = Organisation for Economic Co-operation and Development.

APPENDIX 3

PRISMA Flowcharts

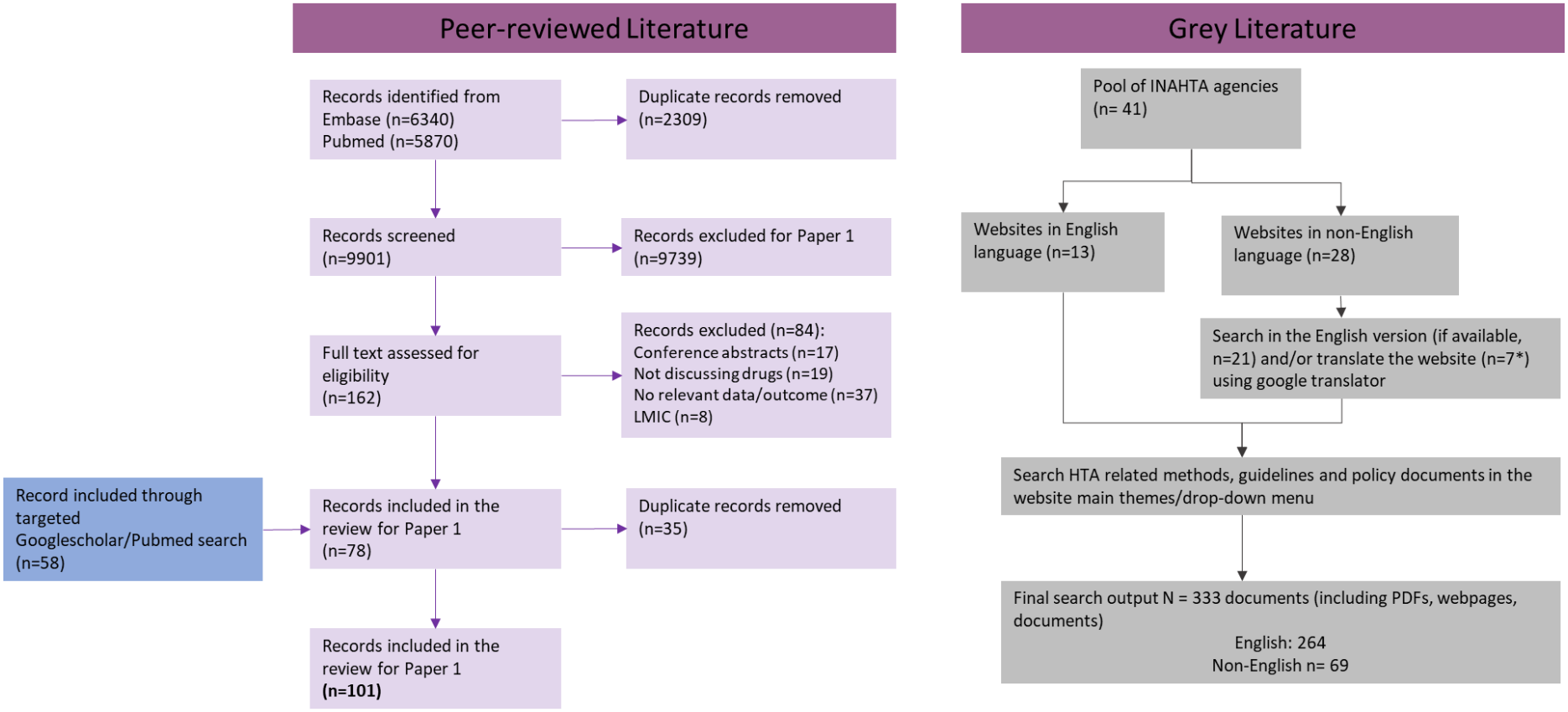

Figure 34 PRISMA flow chart for Paper 1

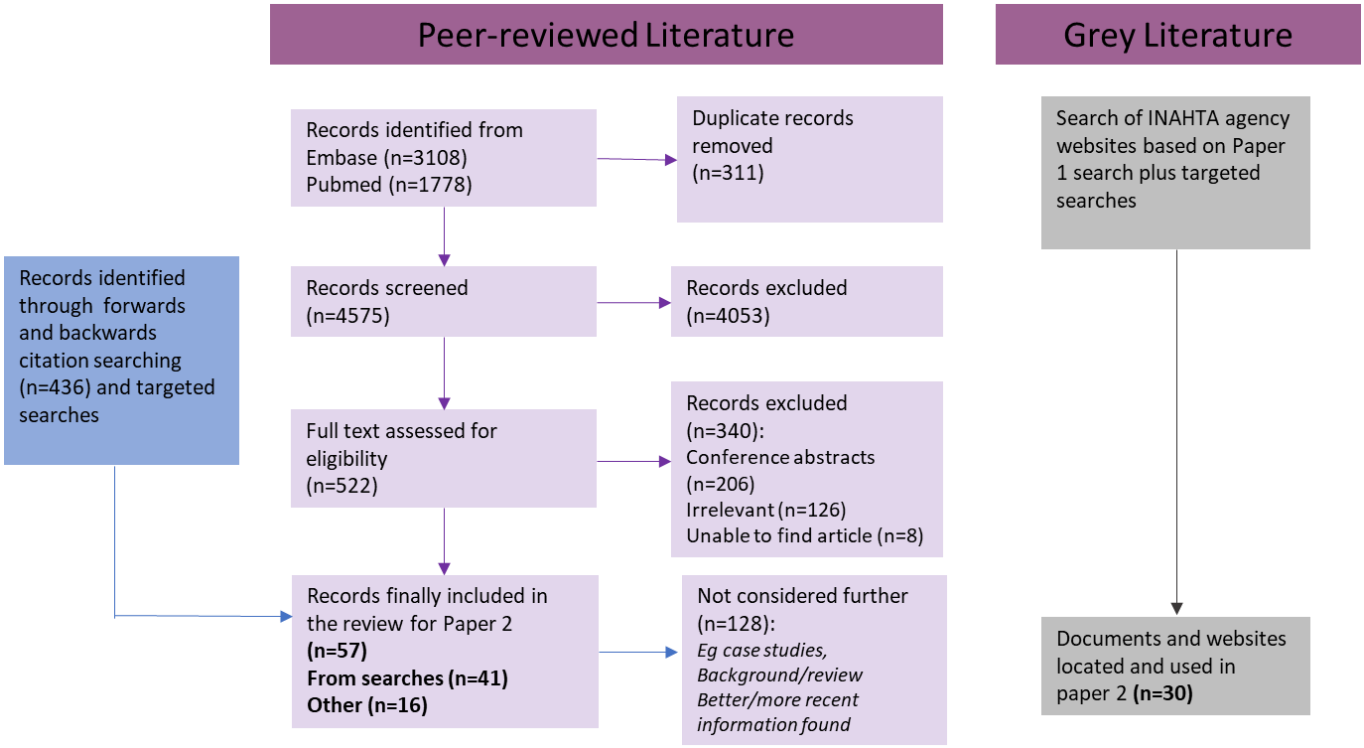

Figure 35 PRISMA flow chart for Paper 2

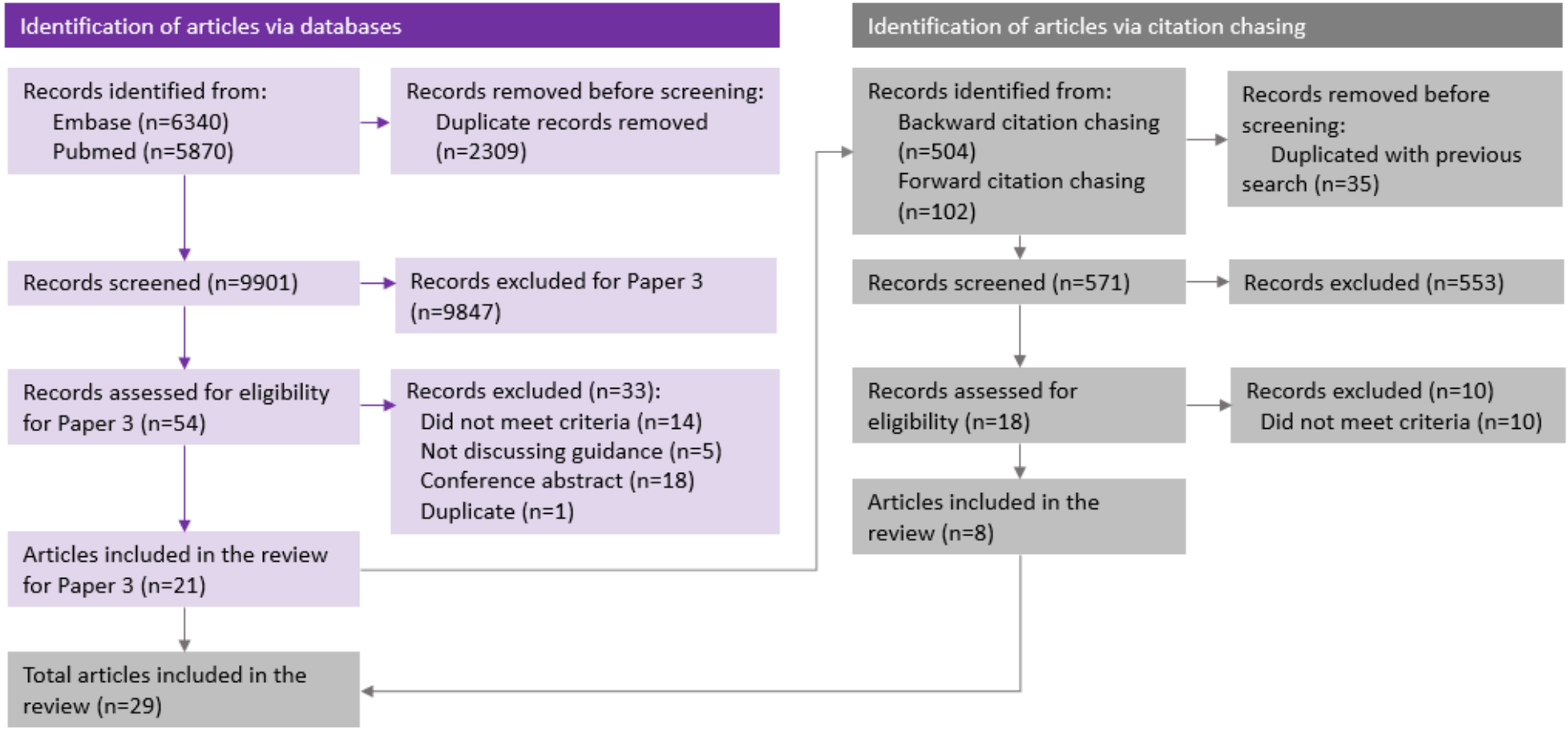

Figure 36 PRISMA flow chart for Paper 3

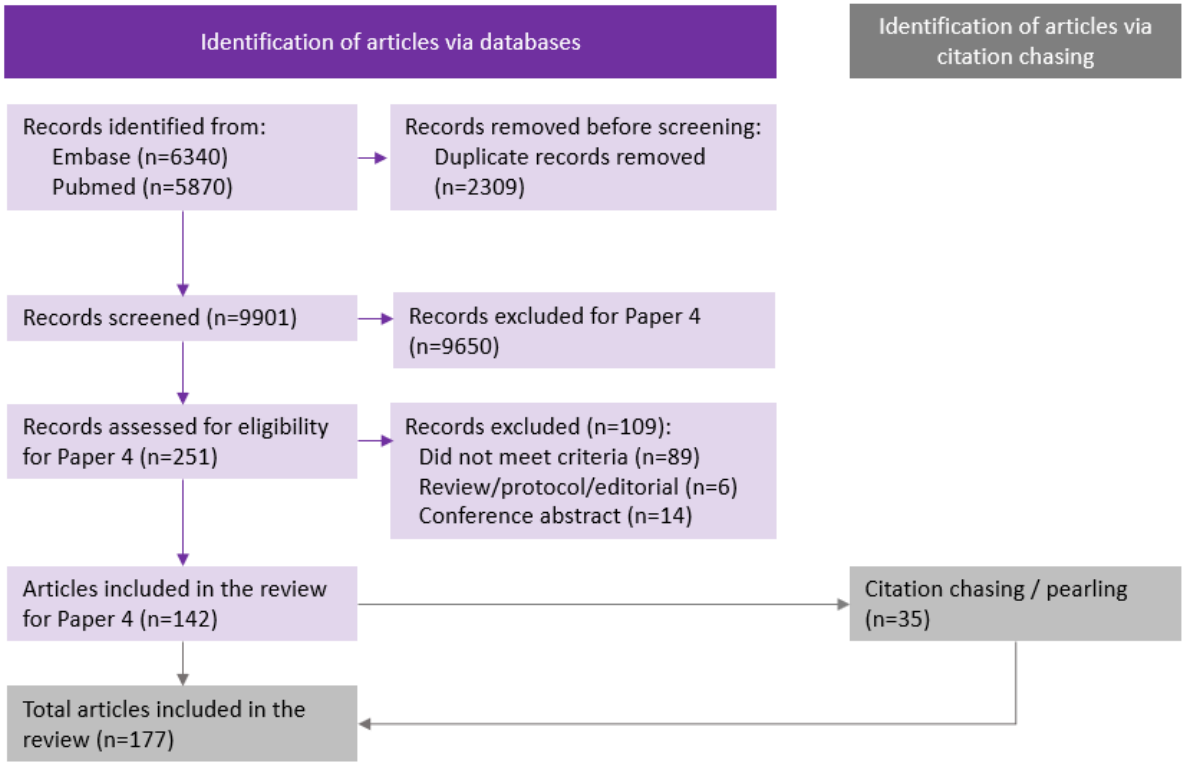

Figure 37 PRISMA flow chart for Paper 4

APPENDIX 4

Surrogate endpoints used by the FDA

Table 77 Surrogate Endpoints That Were the Basis of Drug Approval or Licensure (FDA, 2023)

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
Achondroplasia	Patients with achondroplasia	Annualized Growth Velocity	Accelerated	C type natriuretic peptide	5 years and older
Acromegaly	Patients with acromegaly who don't respond to or cannot undergo other standard therapies	Serum Insulin-like growth factor-I (IGF-1)	Traditional	Growth hormone receptor antagonist	2 years to less than 18 years
Acute bronchospasm	Patients with acute bronchospasm associated with reversible obstructive airway disease or exercise	Forced expiratory volume in 1 second (FEV_1)	Traditional	Beta-2 adrenergic agonist	5 years and older
Asthma	Patients with asthma	Forced expiratory volume in 1 second (FEV_1)	Traditional	Corticosteroid; Beta-2 adrenergic agonist; Anticholinergic	4 years and older
Nonmalignant hematology	Patients with thrombocytopenia due to immune (idiopathic) thrombocytopenia or chronic hepatitis C	Platelet count	Traditional	Thrombopoietin receptor agonist	1 year and older
Nonmalignant hematology		Serum ferritin and liver iron concentration	Traditional§	Iron chelator	2 years or older for chronic iron overload and 10 years older for non-transfusion-dependent thalassemia syndromes
Nonmalignant hematology	Patients with severe aplastic anemia	Hematologic response	Traditional	Thrombopoietin receptor agonist	1 year and older
Nonmalignant hematology	Patients with methemoglobinemia	Serum methemoglobin	Accelerated	Oxidation-reduction agent	All pediatric age groups
Cancer: hematological malignancies	Patients with acute lymphoblastic leukemia; B-cell lymphoma	Durable objective overall response rate (ORR)	Accelerated/Traditional§	Mechanism agnostic*	1 to 21 years

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
Cancer: hematological malignancies	Patients with acute lymphoblastic leukemia	Event-free Survival	Accelerated/Traditional§	Mechanism agnostic*	1 to 21 years
Cancer: hematological malignancies	Patients with chronic myeloid leukemia	Major hematologic and cytogenic response	Accelerated/Traditional§	Mechanism agnostic*	3 to 20 years
Cancer: hematological malignancies	Patients with Acute Lymphoblastic Leukemia	Serum Asparaginase	Traditional	Asparagine-specific enzyme	All pediatric age groups
Cancer: solid tumors	Patients with tuberous sclerosis complex with subependymal giant cell astrocytoma; merkel cell carcinoma; neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation; thyroid cancer; tumour mutational burden high solid tumours; neuroblastoma	Durable objective overall response rate (ORR)	Accelerated	Mechanism agnostic*	28 days and older
Cancer: solid tumors	Patients with metastatic melanoma	Progression-free survival	Accelerated	Mechanism agnostic*	12 years and older
Chagas disease	Patients with Chagas disease	Immunoglobulin G antibody negative or least 20% decrease in optical density on two different IgG antibody tests against antigens of *T. cruzi*	Accelerated	Antimicrobial	Birth to less than 18 years of age
Chronic kidney disease	Patients with chronic kidney disease secondary to multiple etiologies	Estimated glomerular filtration rate or serum creatinine	Traditional	Mechanism agnostic*	
Cystinuria	Patients with cystinuria	Urinary/urine cystine	Traditional	Reducing and complexing thiol	-
Cystic fibrosis	Patients with cystic fibrosis	Forced expiratory volume in 1 second (FEV_1)	Traditional	Cystic fibrosis transmembrane conductance regulator potentiator	2 years and older
Hyperkalemia	Patients with hyperkalemia	Serum potassium	Traditional	Potassium binder	

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
Cytomegalovirus (CMV)	CMV seropositive and hemotopoietic transplant recipients requiring prophylaxis	Plasma CMV-DNA exceeding threshold for starting treatment	Traditional	Antiviral	12 years and older
Diphtheria vaccine (in combination vaccines)	Persons to be immunized against diphtheria	Anti-diphtheria toxoid antibody	Traditional	Induction of immunity	6 weeks and older
Diphtheria, tetanus, pertussis, polio, haemophilus type b disease, and hepatitis B vaccine	Patients to be immunized against diphtheria, tetanus, pertussis, polio, haemophilus type b disease, and hepatitis B vaccine	Neutralizing antibody	Traditional	Induction of immunity	6 weeks to less than 5 years of age
Duchenne muscular dystrophy (DMD)	Patients with DMD who have a confirmed mutation of the DMD gene that is amenable to exon skipping	Skeletal muscle dystrophin	Accelerated	Antisense oligonucleotide	Mean age 8.9 years
Exocrine pancreatic insufficiency	Patients with exocrine pancreatic insufficiency due to cystic fibrosis	Fecal coefficient of fat absorption	Traditional	Pancreatic enzymes that catalyze the hydrolysis of fats, proteins, and starches.	6 months and older
Fabry disease	Patients with confirmed Fabry disease	Complete/ near complete clearance of GL-3 inclusions in biopsied renal peritubular capillaries (using the Fabrazyme Scoring System)	Traditional	Enzyme replacement therapy	2 years and older
First aid antiseptic; Health care antiseptic; Consumer antiseptic	General public, consumers, and health care professionals	Bacterial count	Traditional and Monograph	Antimicrobial	All pediatric age groups
Haemophilus B conjugate vaccine	Persons to be immunized against Haemophilus B	Anti-polyribosyl-ribitol-phosphate antibody concentrations	Accelerated	Induction of immunity	6 weeks to 71 months

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
Hepatitis A (Hep A) vaccine	Persons to be immunized against Hep A	Anti-Hep A antigen antibody	Traditional	Induction of immunity	12 months and older
Hepatitis B (Hep B) vaccine	Persons to be immunized against Hep B	Anti-Hep B antigen antibody	Traditional	Induction of immunity	All pediatric age groups
Hepatitis B Virus (HCV)	Patients with HBV	Undetectable plasma HBV-DNA for indefinite treatment or HBsAg loss for finite treatment	Traditional	Antiviral	2 years and older
Hepatitis C Virus (HCV)	Patients with HCV with or without cirrhosis	Sustained viral response (HCV-RNA)	Traditional	Antiviral	3 years and older
Homozygous sitosterolemia (phytosterolemia)	Patients with homozygous sitosterolemia (phytosterolemia)	Plasma sitosterol and campesterol	Traditional	Dietary cholesterol absorption inhibitor	
Human Immunodeficiency Virus-1 (HIV-1)	Patients with HIV-1	Undetectable plasma HIV-RNA	Traditional	Antiviral	Patients infected since birth
Human Immunodeficiency Virus-1 (HIV-1)	Highly treatment experienced HIV-1 patients	Greater than 0.5 log reduction in plasma HIV RNA	Traditional	Antiviral	Patients infected since birth
Human papillomavirus	Persons to be immunized against human papillomavirus	Cervical intraepithelial neoplasia	Traditional	Induction of immunity	9 through 17 years
Hypercholesterolemia	Patients with heterozygous familial hypercholesterolemia	Serum LDL-C	Traditional	Lipid-lowering	
Hypercholesterolemia	Patients with homozygous familial hypercholesterolemia	Serum LDL-C	Traditional	Lipid-lowering	
Hyperphosphatemia	Patients with chronic kidney disease on dialysis with hyperphosphatemia	Serum phosphate	Traditional	Phosphate binder	-
Hypertension	Patients with hypertension	Blood pressure	Traditional	Mechanism agnostic*	-
Hypokalemia	Patients with hypokalemia	Serum potassium	Traditional	Potassium salts	
Hyponatremia	Patients with hypervolemic and euvolemic hyponatremia	Serum sodium	Traditional	Vasopressin receptor antagonist	
Meningococcal B vaccine	Persons to be immunized against	Serum bactericidal antibody	Traditional	Induction of immunity	10 to 25 years

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
	meningococcal meningitis				
Hypothyroidism	Patients with hypothyroidism	Thyroid-stimulating hormone (TSH)	Traditional	Thyroid hormone analog	
Influenza A H5N1	Persons to be immunized against influenza	Hemagglutination inhibition antibody	Traditional	Induction of Immunity	6 months and older
Influenza vaccine	Persons to be immunized against influenza	Hemagglutination inhibition antibody	Accelerated	Induction of immunity	6 months and older
Japanese encephalitis vaccine	Persons to be immunized against Japanese encephalitis	Neutralizing antibody	Traditional	Induction of immunity	2 months and older
Lipodystrophy	Patients with congenital or acquired generalized lipodystrophy	Serum hemoglobin A1C , fasting glucose and triglycerides	Traditional	Leptin analog	
Lysosomal Acid Lipase (LAL) deficiency	Patients with LAL deficiency	Serum LDL-c levels	Traditional	Hydrolytic lysosomal cholesteryl ester and triacylglycerol-specific enzyme	Birth to less than 18 years of age
Meningococcal (serogroups A, C, Y, W) meningitis vaccine	Persons to be immunized against meningococcal meningitis	Serum bactericidal antibody	Traditional	Induction of Immunity	2 years and older
Meningococcal A C Y W-135 vaccine	Persons to be immunized against meningococcal meningitis	Serum bactericidal antibody	Traditional	Induction of immunity	2 months and older
Methylmalonic acidemia	Patients with acute hyperammonemia due to methylmalonic acidemia	Plasma ammonia	Traditional	Carbamoyl Phosphate Synthetase 1 activator	Birth to less than 18 years of age
N-acetylglutamate Synthase (NAGS) deficiency	Patients with hyperammonemia due to NAGS deficiency	Plasma ammonia	Traditional	Carbamoyl Phosphate Synthetase 1 activator	Birth to less than 18 years of age
Nonmalignant hematology	Patients with sickle cell disease	Hemoglobin response rate	Accelerated	Hemoglobin S polymerization inhibitor	4 years and older
Pertussis (in combination vaccines)	Persons to be immunized against pertussis	Serum antibody concentrations	Traditional	Induction of immunity	6 weeks and older
Phenylketonuria	Patients with hyperphenylalaninemia due to tetrahydrobiopterin-	Plasma phenylalanine	Traditional	Phenylalanine hydroxylase activator	1 month to less than 18 years of age

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
	responsive phenylketonuria				
Polio vaccine	Persons to be immunized against polio	Neutralizing antibody	Traditional	Induction of immunity	6 weeks and older
Precocious puberty	Patients with central precocious puberty	Serum luteinizing hormone	Traditional	Gonadotropin releasing hormone (GnRH) agonist	
Primary glomerular diseases associated with significant proteinuria	Patients with primary glomerular disease associated with significant proteinuria	Proteinuria (urinary protein/creatinine ratio) *	Accelerated	Mechanism agnostic*	
Primary hyperoxaluria type 1 (PH1)	Patients with primary hyperoxaluria type 1 (PH1)	Urinary oxalate	Traditional	siRNA against hyroxyacid oxidase 1 gene	
Propionic acidemia	Patients with acute hyperammonemia due to propionc acidemia	Plasma ammonia	Traditional	Carbamoyl Phosphate Synthetase 1 activator	Birth and older
Pulmonary Arterial Hypertension	Patients with PAH	Pulmonary vascular resistance	Traditional	Endothelin receptor antagonist	Any age children if there is an approved use in adults and the drug lowers PVR in adults.
Pulmonary Tuberculosis (TB)	Patients with active pulmonary tuberculosis	Sputum culture conversion to negative	Accelerated	Antimicrobial	5 years and older
Rabies immune globulin	Patients with suspected exposure to a rabid animal	Rabies neutralizing activity and antibody response	Traditional	Passive immunity	
Rabies vaccine	Persons to be immunized against rabies	Neutralizing antibody	Traditional	Induction of immunity	All pediatric age groups
Secondary hyperparathyroidism associated with chronic kidney disease	Patients with secondary hyperparathyroidism associated with chronic kidney disease	Serum intact parathyroid hormone (iPTH)	Traditional	Vitamin D analog	
Tetanus vaccine (alone or in combination vaccines)	Persons to be immunized against tetanus	Anti-tetanus toxoid antibody	Traditional	Induction of Immunity	6 weeks and older
Tick-borne encephalitis vaccine	Persons to be immunized against tick-borne encephalitis	Seropositivity by	Traditional	Induction of TBEV-	1 year and older

Disease or Use	Patient Population	Surrogate endpoint	Type of approval appropriate for	Drug mechanism of action	Age range
		neutralization test		neutralizing antibodies	
Type 1 diabetes mellitus	Patients with type 1 diabetes mellitus	Serum hemoglobin A1C	Traditional	Glucose-lowering	6 to 15 years
Type 1 Gaucher disease	Patients with type 1 Gaucher disease	Spleen volume, liver volume, hemoglobin and platelet count	Traditional	Hydrolytic lysozomal glucocerebrosid e-specific enzyme	2 to 17 years
Type 2 diabetes mellitus	Patients with type 2 diabetes mellitus	Serum hemoglobin A1C	Traditional	Glucose-lowering	10 to 16 years
X-linked hypophosphatemi a	Patients with X-linked hypophosphatemia	Serum phosphate	Traditional	Fibroblast growth factor 23 inhibitor	1 year and older
Yellow fever vaccine	Persons to be immunized against yellow fever	Neutralizing antibody	Traditional	Induction of immunity	9 months and older

Source: USA Food and Drugs Administration, https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure, accessed 27 July 2023.

APPENDIX 5

NICE Technical Support Documents

The current NICE guidelines[27] mention 9 technical documents. However, there are currently 22 technical support documents on Sheffield's website (https://www.sheffield.ac.uk/nice-dsu/tsds) (one of the three Universities that make up the Decision Support Unit).

These are:

Table 78 HTA Technical Support Documents available from the University of Sheffield

TSD 1	Introduction to evidence synthesis for decision making
TSD 2	A general linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials
TSD 3	Heterogeneity: subgroups, meta-regression, bias and bias-adjustment
TSD 4	Inconsistency in networks of evidence based on randomised controlled trials
TSD 5	Evidence synthesis in the baseline natural history model
TSD 6	Embedding evidence synthesis in probabilistic cost effectiveness analysis: Software choices
TSD 7	Evidence synthesis of treatment efficacy in decision making: a reviewer's checklist
TSD 8	An introduction to the measurement and valuation of health for NICE submissions
TSD 9	The identification, review and synthesis of health state utility values from the literature
TSD 10	The use of mapping methods to estimate health state utility values
TSD 11	Alternatives to EQ-5D for generating health state utility values
TSD 12	The use of health state utility values in decision models)
TSD 13	Identifying and reviewing evidence to inform the conceptualisation and population of cost-effectiveness models
TSD 14	Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data
TSD 15	Cost-effectiveness modelling using patient-level simulation
TSD 16	Adjusting survival time estimates in the presence of treatment switching
TSD 17	The use of observational data to inform estimates of treatment effectiveness in technology appraisal: Methods for comparative individual patient data
TSD 18	Methods for population-adjusted indirect comparisons in submissions to NICE
TSD 19	Partitioned survival analysis as a decision modelling tool
TSD 20	Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints
TSD 21	Flexible methods for survival analysis
TSD 22	Mapping to estimate health state utilities

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Attachment 1 - Health Technology Assessment Policy and Methods Review

HTA Pathways and Processes, Clinical Evaluation Methods and Horizon Scanning Supplementary Data – detailed country profiles

March 2024

make history.

TABLE OF CONTENTS

DETAILED COUNTRY PROFILES

AUSTRALIA

- **Equity**

Australia's MSAC Guidelines [1] explicitly state that groups defined by "age, socioeconomic status or geographical location" may be impacted differently by funding a health technology and that this is an "equity" consideration for MSAC. The Guidelines also invite sponsors to identify how funding the health technology might increase "equity of access" and decrease any health disparities "resulting from differences in access to care in rural and remote areas or … unmet clinical need". The Guidelines also state that MSAC may need to consider the "rule of rescue", which is the idea (not captured by conventional economic evaluation) that there is a special moral imperative to rescue identifiable individuals from death. The Guidelines also imply that including "production gains" in economic evaluation problematically favours people who can and choose to contribute to "societal production" (e.g., work).

Australia's PBAC Guidelines [2] refer to "access or equity" and repeat MSAC's mention of "age, or socioeconomic and geographical status" as related considerations, as well as the "rule of rescue" and "production gains", as per MSAC.

- **Stakeholder engagement**

Australia's MSAC Guidelines [1] state that the "best available evidence" includes evidence provided by "experts" and evidence "informed by consumer engagement". Those developing evidence collection parameters ("PICO confirmation developers") should seek feedback from the advisory committee "and other stakeholders". Published literature on the "perspectives of the patient and other stakeholders" may be relevant, with "the views and perspectives of consumers, patients or members of the public obtained through public consultation". Meanwhile, PBAC "considers submissions from industry sponsors … medical bodies, health professionals, and private individuals and their representatives" [2].

A "pilot mentoring program is currently being designed" within government to upskill consumer representatives [3]. Research has found that "consumers want timely access to new medicines, but not at the expense of safety, efficacy, equity and sustainability" [4]. Research suggests "there is a growing discussion" about the importance of increasing transparency in Australian HTA to aid "healthcare stakeholders such as patients and physicians" and to "improve processes for jurisdictions that have less capacity for HTA" [5]. Research suggests that in 2014-2016 PBAC permitted a 10-minute industry presentation for 28% of major submissions and at 78% of those hearings a "clinician external to the sponsor" also presented [6]. PBAC considered only "45% of sponsor hearings to be informative or moderately informative whereas 18% were classed as uninformative" [6].

The below table summarises stakeholder engagement in Australia and is copied from [7].

Australia has both formal and informal ways of engaging with clinicians. Academic groups provide most of Australia's HTA evaluations and are contracted to provide a range of other advice when required. Both MSAC and PBAC consult around specific technologies.

Stakeholder engagement	HTA committee representation	Patient involvement	Appeals	Transparency
- Manufacturers have two opportunities for input: pre-subcommittee response and pre-PBAC response **- Manufacturers can present comments to PBAC in form of a hearing** **- Stakeholder meetings may be held if PBAC issues a negative recommendation but the drug treats a serious, disabling, or life-threatening condition with no other treatment option**	Members include doctors, health professionals, health economists, and consumer reps appointed by the Australian government	HTA consumer consultant committee has several key roles: - Assist Department of Health to work more closely with consumers in HTA decision-making - Bring consumer evidence into HTA processes - Inform policy on consumer and patient matters in HTA - Create opportunities for better public understanding of HTA - Enhance methods for formal patient inputs	- No appeals - Manufacturers can request independent review (very rare) - No new information is allowed in review, which is conducted by single expert reviewer - Manufacturers can resubmit with new evidence or change to indication or restrictions	- PBAC decisions and summary documents published online - Committee agenda, minutes, and deliberations posted online - HTA committee members must disclose COI annually

AUSTRIA

The Austrian health system is complex, with responsibilities shared between states and the federal level, and some of these responsibilities are delegated to self-governing bodies providing social health insurance. The health care system follows a mixed-payer financing model, with federal, state and social insurance funds contributing to the health budget. The federal government is responsible for the regulation of the provision of health care and social insurance, whereas state governments are responsible for specifics of implementation and legislation. More than 75% of the current healthcare budget is provided by public sources, which comprise income-related social health insurance (SHI) (60%) and general taxation (40%). Approximately 18% of the health care

expenditure is out-of-pocket payment. The coverage of SHI is nearly universal (99.9%), with no competition between different insurance funds, as an assignment to a particular fund depends upon the type and place of employment [8].

- **HTA Model**

Various academic and non-academic institutions perform HTA in Austria at the request of a sponsor, including the National Insurance Organisation (HVB), the Austrian Public Health Institute (Gesundheit Österreich GmbH, GÖeG) and the Austrian Institute for Health Technology Assessment (AIHTA) (formerly known as the Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)). In Austria, the HTA process occurs in response to sponsors' submissions and is therefore reactive [8].

The pharmaceuticals sponsors apply for reimbursement by submitting their dossier to HVB, which conducts the HTA using evidence provided by the sponsor for reimbursement decision-making. In some cases, HVB can commission HTA groups such as AIHTA to carry out its own HTA and identify the evidence to use and provide recommendations for reimbursement. These recommendations are then submitted to the Pharmaceutical Evaluation Committee, which comprises different stakeholders including academics, clinicians, pharmacists, the Social Security Institutions, the Austrian Chamber of Commerce, and the Federal Labor Board for appraisal. Based on recommendations received after the assessment and appraisal process, HVB decides whether to include the drug in the positive list. Due to the transparency directive, the final decision in Austria must be made within 180 days [7].

Based on the dossier submitted by the sponsor, the Pharmaceutical Evaluation Board of the HVB assesses the added therapeutic value and cost-effectiveness of the drug. Drugs suggesting a significant added therapeutic and/or economic value can be classified into green boxes (reimbursable) or light and dark yellow boxes (conditional reimbursement and/or reimbursement under certain circumstances). The dark yellow box (RE1) comprises medicines that can only be reimbursed if approved by the Social Insurance Association. Medicines in the light-yellow box (RE2) can be reimbursed if prescribing physicians indicate the prescriptions are in line with the medicine's use [8].

Disinvestment occurs implicitly in Austria, with no specific pathway for delisting obsolete or low-added-value technologies.

- **Equity**

Austria commissioned a review of its health system that comments extensively on equity, with a focus on delayed access to care for people depending on their age, health, income, employment status, education, socioeconomic background, and geographical location (efficiency-review-of-austrias-social-insurance-and-healthcare-system). The report was informed by engagement with academics, professional societies and patient advocacy groups.

- **Stakeholder engagement**

In 2016 Austria noted that its citizens and patients had "only been involved in health and care policy decisions very sporadically and unsystematically" [9]. Austria has engaged HTA agencies, regulatory bodies, payers, patient groups, clinicians, manufacturers and other experts across Europe to produce guidance on a framework for funding orphan drugs [10]. Austrian guidelines for using Real-World Evidence (RWE) also emphasise the importance of stakeholder engagement [11].

- **Special Pathways**

Austrian Social Insurance decides to incorporate a specific drug into the Reimbursement Code at a determined reimbursement price through negotiation with the market authorisation holder (MAH). In most cases, the negotiation results in financial-based managed-entry agreements (MEA) for high-cost drugs. The nature and details of such agreements are confidential, but the drugs are flagged as MEA drugs in the Reimbursement Code unless MAH oppose the publication of the labelling [12, 13].

In general, HTA assessment is not applicable to in-patient or hospital products. As many ATMPs, including those for rare disease, are currently designated as in-patient products, they usually undergo HTA and price negotiation only on a hospital-by-hospital basis. But such negotiations can be inconsistent and may not be feasible for many hospitals due to time and resource constraints. No special pathway exists for the reimbursement of drugs for rare diseases. However, in some cases, drugs for rare diseases have occasioned a special reimbursement arrangement on an individual basis. The overall access to orphan drugs (including ATMPs) is uncertain [10].

BELGIUM

Belgium has a multi-payer health care system in which 99% of the population is covered by compulsory health insurance and 1% by a public centre for social assistance [14]. People can also pay premiums on voluntary health insurance for extra coverage through a complementary public health insurance component and/or private insurance [14]. The major health care financing comes from the compulsory national health insurance called the sickness fund. The National Institute for Health and Disability Insurance (NIHDI) is the payer of this compulsory health insurance, which the fund comes from tax and individual social contributions [1]. The HTA process in Belgium is in a hybrid model. Sponsors are required to submit reimbursement applications to NIHDI. Therefore HTA is conducted reactively [15]. But the HTA can also be conducted by the Belgian Health Care Knowledge Centre (KCE) at the request of NIHDI, while KCE conducts HTA proactively. The involvement of the other HTA agencies that conduct HTA proactively forms the basis of the hybrid HTA model. The Commission for the Reimbursement of Medicinal Products (CRP) under the NIHDI, conducts HTA appraisal and makes recommendations [15].

- **HTA pathways**

The HTA process is strictly performed within a pre-defined timeline under NIHDI remit. Since the NIHDI receive the reimbursement request from the sponsors, the HTA starts

in parallel with the procedure for the maximum price setting of the product. From the time the NIHDI receive the reimbursement request, the HTA report is generated on day 60, HTA recommendations are made on day 150, and the Minister of Social Affairs and Public Health decides on whether the medicine should be included in the positive reimbursement list on day 180 [15]. The reimbursement decision is not 100% bound to the HTA recommendation, where the Minister can deviate from the HTA recommendation for budgetary or social reasons.

- **Flexibility, predictability and transparency of HTA pathways**

Sponsors are required to make claims regarding the therapeutic values of the drugs, which correspond to three types of submissions: class 1, class 2 and class 3. Demonstration of cost-effectiveness is not required for submissions under class 2 or 3, because the proposed medicine under these categories has a similar therapeutic value to the existing comparator or they are the generics. Only a class 1 submission can attract the premium price, because it is required to prove added value to the comparator[16].

The HTA recommendations only fall into two categories: approval and rejection. However, the 'convention' could be proposed by the sponsors, the Minister of Health or the CRP, if the CRP makes a negative HTA recommendation. The convention is the approach of managed entry agreement, which includes information such as the price and reimbursement basis, modalities of managing risk (refund or cap price, etc), and the modalities of revision and extension of the convention. The sponsor and CRP negotiate the convention, and the final HTA recommendations will incorporate the result of these negotiations. If the HTA recommendation still cannot be made, the final assessment report approved by the CRP can be discussed by the working group consisting of representatives of all stakeholders, and the final assessment report will form the basis of the final reimbursement decision[16]. Therefore, although the HTA decisions strictly fall into categories of approval or rejection, the convention provides lots of flexibility in terms of HTA recommendations. Medicines may be rejected initially but can be recommended with the convention. Or medicines may be rejected by the HTA process but still get listed according to the discussion of working groups. The flexibility of the HTA decision is therefore partial. For the work under CRP remit, the predictability and transparency of the HTA process are unknown because there is no information in English was found.

For KCE, HTA is conducted annually; therefore, there is no flexibility in the HTA process. No information was found in the CRP remit regarding the working cycle of HTA.

The KCE report does not provide any recommendations; therefore, the HTA decision under KCE remit is not applicable. The predictability of KCE appraisal is also not applicable. The HTA process under the KCE remit is predictable, and the HTA report is highly transparent. The KCE process book specifies every step that could have been done, including detailed guidance on literature searching, appraisal of different studies, and synthesis[17]. The HTA process is transparent under the KCE remit, where full HTA reports are published online without any redaction.

- **HTA pathways for specific technologies and populations**

To be eligible to apply for convention, as described above, the submissions should be 1) under class 1 categorisation, or 2) indicated for orphan drugs, or 3) indicated for drugs with new indications for unmet need, or 4) where the comparator is under convention [16]. The applicants and the CRP can initiate a convention during the application period. The convention will also specify the consequence of non-compliance with the convention. The convention lasts for a minimum of one year and a maximum of three years. Evaluation will be conducted to determine whether the convention should be kept or removed.

- **Equity**

Belgium invites proposals for HTA-related research prioritisation that focus on "affordability for patients" and "health inequalities" [18], in addition to "fair access to care" [19]. In 2020 Belgium conducted a health system review with a focus on equity for "at-risk groups" and people from diverse cultures and geographical regions, and this review detailed some of the patient and citizen involvement conducted to date [15].

- **Stakeholder engagement**

Belgium has recently begun working with patient groups. Belgium conducted research into "citizen and patient participation in reimbursement decision-making", with "equity" being one reason proposed for such participation [17]. Belgium works with academics on HTA-related research, whose questions and outcomes should be determined with experts and stakeholders, including patients [17]. Belgium regards such patient involvement in research as needed in light of "fundamental ethical" as well as "instrumental and procedural" reasons [17]. There is evidence that Belgian HTA has consulted with experts, clinicians and manufacturers, including for rare diseases [20].

CANADA

The Canadian Medicare health system is decentralised, universal, publicly funded, and administered primarily by the country's 13 provinces and territories. Each has its own insurance plan, and each receives cash assistance from the federal government on a per-capita basis. The provincial and territorial governments have most of the responsibility for delivering health and other social services. The federal government is also responsible for some funding and delivery of primary and supplementary services for certain groups of people (i.e., First Nations people living on reserves; Inuit; serving members of the Canadian Armed Forces; eligible veterans; inmates in federal penitentiaries; and some groups of refugee claimants). Beginning in the mid-1990s, most provinces and territories worked to control costs and improve delivery by decentralising decision-making on health care delivery to the regional or local board level. However, in recent years, some provinces have moved away from a decentralised model of health care delivery in favour of consolidating the number of health authorities and centralising decision-making structures [21].

In 2018, the Advisory Council on the Implementation of National Pharmacare was established, and in the interim report, the council recommended federal, provincial, and territorial governments collaborate to create a new arms-length Canadian drug agency to oversee national pharmacare [21].

CADTH

Canada's Drug and Health Technology Agency (CADTH), provides independent, nonbinding information and advice for the country's publicly funded healthcare systems (except in Quebec). CADTH oversees two pan-Canadian HTA processes in Canada: the CADTH pan-Canadian Oncology Drug Review (pCODR) and the CADTH Common Drug Review (CDR). The pCODR primarily focuses on evaluating oncology drugs, whereas the CDR focuses on all other medicine types. Each program has separate independent expert committees that provide reimbursement recommendations. For the CDR, these recommendations are directed to federal, provincial, and territorial drug plans, except for Quebec. As for pCODR, in addition to federal, provincial, and territorial drug plans, provincial cancer agencies also receive the recommendations. In Quebec, INESSS evaluates the clinical and cost effectiveness of healthcare technologies, medications, and interventions to advise the Quebec public drug plan on their adoption, usage, and coverage [22].

The current CADTH reimbursement review process is initiated by an eligible sponsor, namely a pharmaceutical company. Currently under consideration are proposals for a non-sponsored reimbursement review process (for public drug program requests where the sponsor declines to file a submission) and for new streamlined drug class reviews (a form of therapeutic review leveraging existing published evidence and analyses).

Provincial and Territorial (P/T) Governments (except Quebec)

Following CADTH recommendations for the national Common Drug Review (CDR for non-cancer drugs, and pCODR for cancer drugs), each provincial and territorial (P/T) government participating in the process makes a funding decision. For instance, Alberta's Expert Committee on Drug Evaluation and Therapeutics (ECDET) assesses medicinal products and provides recommendations to the Minister of Health concerning reimbursement. Any medicines that do not qualify for review under the CDR Procedure or the Expedited Review Procedure undergo an assessment by the Expert Committee on Drug Evaluation and Therapeutics (ECDET) before their inclusion in the Alberta Drug Benefit List (ADBL). The Ministry of Health (Alberta) works together with health evidence revie Following CADTH recommendations for the national Common Drug Review (CDR for non-cancer drugs, and pCODR for cancer drugs), each provincial and territorial (P/T) government participating in the process makes a funding decision. For instance, Alberta's Expert Committee on Drug Evaluation and Therapeutics (ECDET) assesses medicinal products and provides recommendations to the Minister of Health concerning reimbursement. Any medicines that do not qualify for review under the CDR Procedure or the Expedited Review Procedure undergo an assessment by the Expert Committee on Drug Evaluation and Therapeutics (ECDET) before their inclusion in the

Alberta Drug Benefit List (ADBL). The Ministry of Health (Alberta) works together with health evidence review partners like the Institute of Health Economics (IHE), the University of Alberta Health Technology and Policy Unit, the University of Calgary, the Health Technology Assessment Unit, and CADTH. If there is a need to reevaluate medicines that were not initially approved by the Canadian Expert Drug Advisory Committee and ECDET review processes, the Ministry of Health retains the authority to implement the Product Listing Agreements (PLA) policy. These PLAs may encompass various forms, such as a Price/Volume Agreement, Coverage with Evidence Development Agreement, Utilisation Management Agreement, and Health Research Capacity Development Agreement w partners like the Institute of Health Economics (IHE), the University of Alberta Health Technology and Policy Unit, the University of Calgary, the Health Technology Assessment Unit, and CADTH. If there is a need to reevaluate medicines that were not initially approved by the Canadian Expert Drug Advisory Committee and ECDET review processes, the Ministry of Health retains the authority to implement the Product Listing Agreements (PLA) policy. These PLAs may encompass various forms, such as a Price/Volume Agreement, Coverage with Evidence Development Agreement, Utilisation Management Agreement, and Health Research Capacity Development Agreement [23].

In Ontario, the Ministry's expert advisory committee is responsible for evaluating submissions for funding. Subsequently, the committee provides recommendations to the Executive Officer of Ontario's drug programs. The final funding decision is made by the Executive Officer, taking into account the committee's recommendation, the government's budget for drug programs, and the public's best interest.

Quebec

In Quebec, the regional healthcare services are funded through general taxation, revenues generated from income taxes and other taxes, and contributions made by employers and individuals into the Health Services Fund. The insurance plans comprise the Hospital Insurance Plan and the Health Insurance Plan. A Public Prescription Drug Plan is compulsory for the residents of Quebec, which is a joint plan for universal coverage based on partnership between private insurers and the State. Moreover, children under the age of 18 staying in Québec temporarily for more than 6 months are also covered [24].

INESSS

The Institut National d'excellence en santé et en services sociaux (INESSS) is responsible for evaluating medicine submissions for reimbursement and providing recommendations to the Minister of Health and Social Services for updating the formulary for the basic drug insurance plan (referred to as the List of Medicines).

Just like CADTH, INESS also has different type of reviews such as standard review of new drugs and drugs with new indications, and tailored and complex reviews. Submissions for new formulations of existing drugs or new combination products, or subsequent-

entry non-biologic complex drugs may qualify for tailored review. On the other hand, the complex review process covers cell and gene therapies, drugs that are first-in-class, drugs reviewed through one of Health Canada's expedited pathways (such as priority review or advance consideration), and drugs that have an undefined place in therapy.

INESSS requires that the manufacturer informs it at least two months prior to its intention to submit an evaluation request.

Any reimbursement review submission may be filed before receiving market authorisation from Health Canada (i.e., pre-NOC submissions) or after (i.e., post-NOC submissions). Pre-NOC submissions may be filed up to 180 calendar days in advance of the anticipated receipt of a NOC or NOC/c (Notice of Compliance (NOC) or Notice of Compliance with conditions (NOC/c)) [25].

- **Flexibility, Predictability and Transparency**

The application process is also flexible. Sponsors are required to provide CADTH with a minimum of 30 business days' notice for anticipated submissions, and applications are typically initiated within 10 business days of being accepted for review by CADTH. The review process includes stakeholder inputs from patient groups, clinician groups and drug programs. Draft recommendations are issued to the sponsor in the targeted timeframe (< 180 calendar days) following CADTH's expert review committee meetings, which are scheduled up to 12 times annually for both non-oncology and oncology drugs.

The final recommendations (reimburse/reimburse with conditions/do not reimburse) and reasons are posted on the CADTH website. Confidential information may be redacted at the request of the sponsor.

Recently, CADTH, NICE and ICER issued a position statement indicating greater transparency of unpublished data in their recommendations and decisions. Under this arrangement, from May 2023, CADTH and NICE will not redact any clinical data that are awaiting publication in their documents. ICER will allow redaction of data that is agreed to be published publicly for 12 months as an academic in confidence [25].

- **Equity**

CADTH views patient engagement as increasing equity, contributing to a fair sharing of resources among health system users [26]. CADTH's Guiding Principle of 'Equity, Diversity, and Inclusion' states that CADTH will foster "health systems that reflect the diverse people of Canada and respond to the self-identified priorities and cultural practices of First Nations, Metis, and Inuit peoples" [27]. CADTH has expressed a commitment to post-market drug evaluation that includes analyses sensitive to sex, gender and First Nations in view of diversity problems in pre-market research. CADTH has shown particular concern for "equitable access to assistive technologies" and "cancer drugs" [26], and for equity implications relating to precision medicine, including how digital technologies may overcome barriers to access to care, especially geographical, with mention of "rural and remote areas". CADTH has also shown particular concern for geographical and socio-economic equity within planning for rural health care [28]. Access to care and

"health status" are both mentioned in relation to equity [29]. There are statements that ethical considerations belong to any Canadian reassessment process, just as equity and fairness are "incorporated in all other HTA processes in Canada" [30].

- **Stakeholder engagement**

CADTH places a major emphasis on stakeholder engagement. Its current Strategic Plan features five guiding principles, including 'Partnership' [27]. CADTH actively builds "meaningful relationships with patient communities (including individual patients, their families and caregivers, and those who represent patients); clinicians; industry; other health organisations; and federal, provincial, and territorial governments" [27].

CADTH extensively details its methods of patient engagement [26], including 17 ways in which it finds patients [31]. Information from patients is used "in all phases" of HTA, including protocol development, "appraisal and interpretation of the evidence, and the development of recommendations" [25]. Information from clinicians is also used in all phases, but especially as drug complexity increases, specifically for "cell and gene therapies" and "first-in-class" products. CADTH has reviewed methods of multi-stakeholder engagement to inform Real World Evidence (RWE) initiatives (sought for "smaller populations or rare disease" [32] and to develop "policies and procedures for multi-stakeholder dialogue for rare diseases", where it regards patient engagement as especially important in view of "limited clinical knowledge" [33].

However, research has found that "despite demonstrated commitment" to public and patient engagement (PPE), "impediments to a unified approach" span CADTH's "organisational history, governance structure, and practices" [34]. Problems include "unclear role descriptions for committee members … differences in philosophy and priority given to PPE", and over-emphasis of "evidence-based principles" to the exclusion of "meaningful integration of patient input" [34]. To help with this, researchers have commended "an acknowledgment of conflicts between multiple epistemic traditions" [34]. (Researchers have commended the same for Australian HTA [35].) Patients groups, for their part, have "expressed considerable uncertainty around the direct impact of their submissions", in spite of CADTH's commitment to transparency [36]. Patient groups also "face substantial resource challenges to prepare submissions, including high opportunity costs and difficulty accessing needed literature and finding relevant patients" [36].

The below table summarises stakeholder engagement in Canada and is copied from [7].

Stakeholder engagement	HTA committee representation	Patient involvement	Appeals	Transparency

- All interested parties can provide feedback (manufacturers, physicians, associations, etc.) - CADTH review team has at least one clinical expert - Drug plans identify issues that may preclude implementation of recommendations	- Appointed by and reports to CADTH President and CEO - Chair plus 14 members (2 public "lay"); members do not represent a specific constituency - Non-member experts may be invited to participate as needed - 66% required for quorum and all members get one vote (chair is tiebreaker); abstention is not allowed	- Call for patient input occurs 20 business days before CDR filing and remains open for 35 business days - Available on CADTH website, e-alert, or Twitter	- Manufacturer can request reconsideration of CDEC decision if 1) recommendation is not supported by evidence submitted or evidence identified in report; 2) CADTH and CDEC failed to act fairly and in accordance with its procedures - No new information can be considered during appeal - Existing recommendations may be revisited as a result of therapeutic review	- Details for HTA process available online - All stakeholders (including patients) must provide COI - Calls for feedback are posted online - All final recommendations are posted online

Canada – INESSS (Quebec)

- **Equity**

INESSS has expressed a commitment to "equitable access for those most in need" in relation to specific technologies [37]. INESSS has also expressed a commitment to "equity" more generally, though without specifying what this means.

- **Stakeholder engagement**

INESSS has an "appointment with the manufacturer" early in its drug evaluation process [38]. INESSS's standing deliberative committees consist of "scientists, clinicians, ethicists, managers and citisens" [39]. INESSS has expressed a general commitment to "further integrating the patient, caregiver and citisen perspectives ... especially for innovative therapies" [40].

Canada – Ontario (HQ)

- **Equity**

Ontario has identified as key "social values" relevant to its work "equity" and "collaboration" [41]. Assessments have included comment on the potential for creating "inequity in access when patients are not able to afford" costs [42]. They have also included examination of "potential health inequities ... considering socially stratifying

factors" [43]. Ontario has sought to engage patients from diverse "geographic, cultural, and socioeconomic" backgrounds in the interests of identifying any important equity implications. Ontario has expressed commitment to "disadvantaged populations or populations in need" as part of assessment [41].

- **Stakeholder engagement**

Ontario has a formal "public and patient involvement framework" that features substantive theory and methodological detail, with several recommendations that have been implemented [44]. When conducting assessments, Ontario routinely engages with clinical experts and conducts original qualitative research with patients with "lived experience" of the therapy, along with their "families and other caregivers" [42]. Assessments have also engaged "ethicists" and "industry representatives" [43], along with "health care providers" and "other health system stakeholders".

However, research into the Ontario and pan-Canadian Common Drug Review found "important areas of disagreement and uncertainty" about the proper role and actual impact of public and patient engagement (PPE) [45]. The researcher proposed that patient and public member positions "may have been created without a good deal of consideration for the different contributions they could make, but many interviewees now see a distinction" [45]. Again, research found that a key concern of patients was "how their input is being used and how it is valued next to clinical and economic evidence" [45]. The researcher found consensus on "the value of having a formal process" for PPE and its potential "to contribute to instrumental goals and make decisions better" [45]. But people remained uncertain on how to best undertake PPE and how to best use its outputs [45].

Canada – IHE (Alberta)

- **Equity**

In Alberta, "equity ... and input from key stakeholders are sometimes considered", including in the form of "equity-weighted population health". This includes distributional impacts and equity of access. The IHE evidences concern for these in thinking through methods for the economic evaluation of personalised medicine [46] and for evaluating policies after they have been implemented [47].

- **Stakeholder engagement**

"Partnership" is one of IHE's five core "values", and the IHE speaks of a "strong history of collaboration with government, health delivery organisations, academia and industry" [47]. The IHE also has a Layperson Advisory Committee, with clear evidence of careful thought as to how to set up and run the committee in line with published best practice [48]. The IHE has reflected its expert advisory group can be improved by increasing access to the right mix of clinicians [49]. And earlier the IHE held multiple discussions on how patients can and should be more involved in HTA. Health Canada has "initiated public engagement on a national strategy to balance equitable access to high-cost drugs for rare diseases with sustainable" expenditure [47]. Stakeholder

engagement seems to have been emphasised more after a 2017 report on precision medicine found that "Top health system delivery problems" included a lack of stakeholder engagement.

- **Special Pathways**

CADTH

As discussed in the above section, high-cost therapies - such as gene or cell therapies, drugs reviewed through expedited pathways and first-in class drugs - undergo complex reviews. However, this is not a completely separate pathway, since complex reviews are similar to a standard review process but evidence is considered from non-randomised trials, there is more consultation with clinical experts, and there is greater consideration of potential ethical and implementation issues [25].

When there is uncertainty regarding the long-term efficacy of a medicine, due to shorter follow up in clinical trials, there is no special pathway for the drug review. However, CADTH can consider the evidence from non-randomised trials in resubmissions in such circumstances. Similarly, there is no specific pathway for the review of co-dependent technologies, but both the diagnostic test/s and drug are simultaneously reviewed through a single submission. There are additional requirements for the submission. The sponsors are required to submit a detailed dossier providing evidence for the clinical utility of the diagnostic tests as well as for the clinical and cost effectiveness of the drug. The pharmacoeconomic evaluation, such as a cost-utility analysis, must also incorporate the cost and consequences of diagnostic tests required for the drug under review [25].

There is no special pathway or process for the assessment of drugs targeting rare diseases, but in the recent framework of standard review, special consideration is given for significant unmet need, encompassing rarity of the condition. A drug approved by Health Canada for the treatment of a rare disease must fulfill certain criteria. It must be life-threatening and seriously debilitating, leading to a reduced lifespan and high burden for caregivers. The incidence must be less than 5 in 10,000 but typically closer to 1 in 100,000, and the disease must be difficult to study due to the small patient population. The CADTH drug review committee may recommend reimbursing such drugs with CED due to the uncertainty in the clinical and pharmacoeconomic evidence alongside the significant unmet need [25].

INESS

There are no special pathways as such. The review process is the same, though checklists for different requirements specific to the type of application are available. For rare diseases, the review process follows the same steps, however the INESS can recommend the conditional reimbursement (e.g. CED) of orphan drugs even with a highly uncertain evidence base to meet a high clinical unmet need.

DENMARK

In Denmark, a decentralised health system exists. The national government provides grants from tax revenue to regional government to deliver healthcare services. Five regional governments are responsible for the planning and delivery of healthcare services. The overall planning, regulation and supervision of health services are carried out at the national government level through the Parliament, the Ministry of Health and different governmental agencies such as the Health Authority, the Medicines Agency, the Patient Safety Authority, and the Danish Agency for Patient Complaints. Eighty percent of the funding for health care services for each region is provided by the state whereas regional government contributes 20 percent.

- **HTA Model**

Different agencies are involved in HTA depending on whether the intervention is intended to be use in an outpatient or inpatient setting. The Danish Medicines Agency (DMA) is responsible for the authorisation of medicines in the Danish market and for deciding which medicines are eligible for reimbursement in an outpatient setting. The DMA is a part of the Danish Ministry of the Interior and Health. All medicines must be authorised by DMA or EMA before they can be accessed in Denmark. The DMA comprises two main centers: the Centre of Medicines Licensing and Pharmacovigilance, and the Centre for Control, Medical Devices and Availability. The Center for Medicines Licensing and Pharmacovigilance is responsible for the clinical and quality assessment of drugs and pharmacovigilance. The DMA provides recommendations in response to the market authorisation holder submitting an application for general or conditional reimbursement of a drug. The reimbursement committee providing advice to the DMA comprises seven members, who are appointed by the Minister of Health and Prevention upon the recommendation of the Regions' Board for Wages and Tariffs [50]. The criteria and methods used to formulate recommendations are not available in English. Moreover, it is also not clear whether DMA conducts HTA assessments in-house or commissions external HTA groups.

The DMA only carries out assessment and makes decisions on the reimbursement of drugs to be used in outpatient settings. A regional Danish Medicines Council (DMC), established in 2017 by Danish regions, informs decision-makers and Amgros (the Danish central procurement agency for all medicines and medical devices in public hospitals) regarding the clinical and cost-effectiveness of new drugs for the Danish hospital sector. Amgros, based on input provided by the Danish Medicines Council, negotiates the process with pharmaceutical companies for use in hospitals [51]. However, hospital-based HTA is not considered in this review.

The DMA is also not responsible for decisions on the reimbursement of vaccines.

Companies can submit their application to the DMA and DMC for assessment no earlier than day 120 of the market authorisation process at the EMA. On day 120, CHMP adopts the initial assessment report, which includes a list of questions for the applicant to

respond to. At this milestone, the applicants can submit their application for assessment by the DMA and DMC for use in different regions [51]. There is no evidence of data sharing between the two processes, but parallel submissions are permitted in Denmark from day 120 of the market authorisation application.

Drugs are granted different types of reimbursement by the DMA, such as general reimbursement for prescription-only medicines or conditional reimbursement, where medicine is reimbursed in certain cases, such as for a specific patient population or indication. In conditional reimbursement, a medicine may not be reimbursed for use outside specified reimbursement conditions [52].

- **Equity**

In Denmark, industry is invited to "describe any problems regarding accessibility and the occurrence of inequality for special patient groups".

- **Stakeholder engagement**

Denmark provides a guide for its patient representatives [53] and details its patient engagement methods, together with its view of what works well. Denmark also invites industry to provide evidence on the patient perspective [51]. Denmark's 2008 HTA Handbook frequently refers to "citizens" but this often refers to "patients as citizens" [54]. The 2008 Handbook also indicates engagement with clinicians and academics, specifically "public authorities, professional groups and interest groups, managements and staff groups within the health care system, experts and researchers in the relevant areas" [54].

FINLAND

Finland's administrative structure comprises three elements: state, provinces and self-governing municipalities. Municipalities are autonomous and responsible for the provision of basic services to all of its residents, such as social and health services and primary education. The healthcare system is decentralised, comprising three tiers in receipt of public funding: municipal, private and occupational healthcare. Municipalities fund all healthcare services except outpatient drugs by collecting income tax, where each municipality decides their rate. National Health Insurance is run by the Social Insurance Institution (SHI), which funds private healthcare, outpatient drugs, occupational healthcare, and sickness and maternity leave allowances through compulsory insurance fees. SHI finances 17% of the total healthcare cost and is funded by the insured (38%), employers (33%) and the state (28%) [55].

- **HTA Model**

After receiving market approval, assessment and reimbursement decisions for outpatient drugs are made by the Pharmaceutical Pricing Board (HILA) at the national level. These decisions are then implemented by the SHI of Finland (KELA). These medicines are co-financed by patients and national funds of KELA. The patients start

receiving reimbursement after paying the initial deductible (€50) of covered medicines each year. There are three levels of reimbursement: basic level (40%), lower special level (65%) and higher special level (100% of the amount exceeding the co-payment of €4.50 for each purchased medicine). The reimbursement levels are determined based on the severity of the disease and the necessity of the drug.

The HILA operates under the Ministry of Social Affairs and Health and comprises three main units: pharmaceutical pricing board, expert group and secretariat. The board makes a final decision on the reimbursement status and wholesale price of drugs. It comprises seven members for a term of three years at a time. The board meets once per month on average but can meet more frequently if required. The expert group also comprises seven members, from the fields of pharmacology, health economics and medicine. The board can request the opinion of the expert group before it formulates its decision. The Secretariat is responsible for the preparation of documentation that is submitted to the board for decision making. The holder of the market authorisation applies for confirmation of reimbursement status and a reasonable wholesale price for the drug from HILA. The application for basic reimbursement (40%) must include justification of the clinical need for the medicine and a summary of the clinical study results, for example on the medicine's benefits and adverse effects, expected sales volumes, and economic evaluation. For special reimbursement status or reimbursement of a new dosage, the economic evaluation is not required but the applicant can choose to submit it [56].

If the medicine is included in a reference price group, the decision on reimbursement is based on price notifications submitted by the market authorisation holder (MAH) four times per year. If the MAH does not submit the price notification within the specified time, the drug reimbursement status will be terminated at the start of the reference price period. Moreover, if the requirement for forming a reference group is not fulfilled at the start of a new reference price period, the reference price group will cease to exist. When the reference group is terminated, the included drugs will continue to have reimbursement status and their wholesale price for one year (referred to as the transition period). For the continual reimbursement of the drug, the MAH needs to submit a new application for reimbursement status and wholesale price during the transition period [56].

- **Flexibility, Predictability and Transparency**

In certain cases, when there is uncertainty in the total costs, cost-effectiveness and therapeutic value of new drugs, the HILA allows conditional reimbursement. The applicant can propose the conditional reimbursement as part of the application process or when HILA requests additional information after the application has already been discussed in a meeting. In the proposal, the applicant must show that the drug is required for an unmet clinical need and discuss the key uncertainties and how they could be controlled. In the proposal, the applicant must request the suspension of further processing of their application while the applicability of the conditional

reimbursement is examined [57]. If conditional reimbursement status is confirmed by the HILA, a confidential agreement is created between PPB and MAH outlining the conditions of reassessment and controlling the uncertainties associated with the drug. Most of these are financial agreements with arrangements to rebate KELA following criteria specified in the agreement.

There are no documents available providing the details of the HTA process adopted for reimbursement decision-making. Guidelines for preparing applications for reimbursement status and reasonable wholesale price are available. However, it is not clear what characteristics of the evidence base would influence the decision-making process.

The HILA publishes monthly notices of new products reimbursable at the basic or special rate of reimbursement, applications received, meeting resolutions, and a list of products approved and included in the reimbursement system. However, the details of the HTA assessment process are not published.

- **Equity**

There is research evidence that new cancer medicines are variably available at Finnish hospitals, "leading to significant geographical inequity in cancer care" [58]. Concern for equity is evident in government recommendations for medicines policies, especially for costs ever being "borne disproportionately by those less able to afford them", with the observation that medicine use "tends be concentrated in lower socioeconomic and older age groups (mainly with chronic conditions)" [59]. The recommendations also note that, alongside cost-effectiveness, consideration must be given to "patient access and inequity in the light of high user charges in Finland" and "the possibility of geographical inequities" [59].

- **Stakeholder engagement**

There is research evidence that Finnish authorities "do not engage in public discussion about ongoing processes" because they feel that such engagement is made impossible by campaigns "inappropriately" pressuring them to fund some medicines [58]. The Finnish government consulted with government departments, clinician associations, and industry in recommending changes to medicines policies [59].

- **Pathways for Special Technologies**

One of the primary groups of drugs eligible for conditional reimbursement is new pharmacotherapies (with a new active substance) or new indications for drugs already approved for reimbursement. Due to uncertainty about therapeutic value, cost-effectiveness and total costs, drugs with a new active substance or new indications undergo conditional reimbursement agreements. The agreements remain valid for a fixed term, after which reassessment is carried out with additional evidence (if available) to assess reimbursement status. While there are no clear criteria for acceptance in the conditional reimbursement scheme, it seems to depend on a special high unmet clinical need for the drug.

There is no difference in the assessment process of drugs based on their orphan drug status. Drugs for rare disease can be assessed through an inpatient or outpatient drugs route.

FRANCE

The Haute Autorité de santé (HAS) is an independent centralised national HTA body comprised of eight committees that provides scientific advice on health products and technologies for reimbursement recommendations [60]. The transparency committee (TC) undertakes the assessment and makes recommendations for medical products, and the Economic and Public Health Committee (CEESP) undertakes the economic assessment[61]. HTA is mandatory for the drug to be listed, and sponsors are required to submit a drug evaluation dossier to TC to start HTA. Therefore the HTA process is reactive in France for medicines[62]. The TC utilises a reactive approach to evaluating new medicines for the purpose of making reimbursement recommendations (HAS opinions) on a positive listing [63, 64].

According to the Pricing & Reimbursement of Drugs and HTA policies in France published in 2014, it takes 90 days to get HAS opinions [64]. The early access pathway allows prioritisation of HTA for an indication in severe, rare or debilitating conditions. The early access pathway also allows the medicine to be reimbursed before market authorisation, which indicates a parallel working process between regulatory and HTA agencies. However, whether there is a work-sharing process between regulatory and HTA agencies is unknown. There is mention of a disinvestment process, where the medicines are re-assessed every five years [64]. However, details of how the reassessment is conducted are not available in English.

- **Flexibility, Predictability and Transparency**

The elements and criteria related to the HAS opinions are contained in the Transparency Committee doctrine, which includes different evidence requirements, the definition of different assessment outcomes, and features related to different outcomes [65]. However, the explicit threshold for making relevant recommendations is not specified. Meanwhile, although the five factors related to CB outcome are specified in the Transparency Committee doctrine, evidence shows that these five factors disproportionately contributed to the CB outcome, which is mainly driven by the medicine's efficacy and adverse effects [61]. HTA appraisal is unpredictable. However, sponsors may predict the public health impact of medicines to some degree because HAS provides a relevant matrix. HTA evaluation steps are predictable due to the transparency committee doctrine, which specifies the principles of medicines assessment for the reimbursement process.

The final HAS opinions are reportedly sent to all stakeholders, including sponsors, and are required to be published on HAS websites [66]. However, transparency of the HTA process cannot be confirmed because relevant documents are not in English.

- **HTA pathways for specific technologies and populations**

The early access authorisation enables early availability, and reimbursement of medical products indicated for severe, rare or incapacitating diseases that meet these five the following criteria for all: a) there is no other appropriate treatment, b) the initiation of the treatment cannot be deferred, c) the efficacy and safety of the medicinal product are strongly presumed based on the results of clinical trials, d) this medicinal product is presumed to be innovative, notably compared with a clinically relevant comparator [67]. The entry of the early access pathway is also reactive, since which the sponsor needs to lodge an application for the medicines.

There are two types of early access authorisations: pre-MA early access and post-MA early access. The pre-MA early access is suitable for sponsors who have not yet submitted MA applications. The decision of HAS is made following a favourable opinion from The French National Agency for Medicines and Health Products Safety (ANSM) to confirm the strong presumption of efficacy and safety of the medicinal product for the indication in question. ANSM is the National competent authority in France responsible for the MA in France of a medicine that does not get EMA approval [68]. Once pre-MA early access is granted, the sponsor should undertake to submit an official MA application within two years at most [69]. The pre-MA early access reflects an alignment between regulatory and reimbursement processes. The post-MA scheme is for when MA has been granted or when the sponsor has submitted for MA (or will submit within one month).

- **Equity**

France's HAS upholds as core values "equity in access to care" and stakeholder cooperation [70]. In its methods guide for ethical analysis, HAS lists "Equity, Discrimination, Geographical disparity, Social inequality, [and] Accessibility" under the banner of "Justice" [71].

- **Stakeholder engagement**

"Public involvement" is one of the six pillars of HAS's strategic plan, with a focus on the public, patients and carers [70]. In 2019, HAS established the Public Involvement Council [70]. HAS may invite industry, patient associations, and experts to share their opinions [72, 73]. "A public call for applications can also be published on the HAS website" [74]. HAS conducts some "early dialogues", presumably with industry.

Researchers report that in 2017 HAS "created an open, online, systematic contribution process to enable patient and consumer groups (PCGs)" to contribute to HTA [75]. They found that in 2017-2018 79 contributions from 44 PCGs were received for 78 out of the 592 HTAs (13%), with 25% of the medicine HTAs receiving one or more contributions. The contributions covered "quality-of-life aspects, access to care, and personal and family impact" [75]. The PCGs varied greatly in size and budget and were constrained by time and human resources [75].

The below table summarises stakeholder engagement in France and is copied from [7].

Stakeholder engagement	HTA committee representation	Patient involvement	Appeals	Transparency
- Manufacturers submit dossier for assessment - Outside experts may brief HTA committee, but do not attend deliberations or voting - Outside experts cannot represent drug sponsor during adversarial phase	Physicians, patients, and academics 6 members from government agencies have an advisory role	- Stakeholders or interested parties can be approached, including representatives of learned societies and associations of patients and users of the health system - HAS website informs patient and user associations of the purpose and scope of the drug evaluations	- Manufacturer has 10 days following draft notice to comment or ask to be heard by the board; if notice is not given, HAS opinion becomes final - Written observations and hearings give rise to debate in committee; arguments presented are likely to lead to a modification of the opinion	- Final reports are published online, (e.g. May 2019 report) - HTA high-level methods are published, but the basis of actual deliberations is opaque - HTA committee members publish conflict of interest (COI)

IRELAND

Ireland has a publicly financed health system governed by the 2004 Health Act and funded by the State through taxation and social security contributions. Health and social services are provided through the Health Service Executive (HSE), which was established in 2005. The HSE provides health services through a network of providers (such as community health services and hospitals) and through GPs, pharmacists, not-for-profit hospitals and other health professionals contracted by the HSE. The level of health coverage is determined by the Health Act of 1970. The ordinary resident (who has been living or intending to live in Ireland for at least one year) can get either full eligibility for health services if they are medical card holders (category I) or limited eligibility if they are not a card holder (category II). Qualifying for a medical card is dependent on income, age and health status. Card holders (category I) are entitled to free GP services, prescribed drugs subject to a charge per item (€1.50 - €15 per month or €1 - €10 for people aged over 70), public hospital services, specific dental, optical and aural services, maternity and infant care services, and community care. Non-card-holders (category II) are not entitled to free services but may be able to reduce costs with other schemes such as GP visit cards or Drug Payment Scheme cards. Almost half of the population has private health insurance, providing faster access to health services depending upon the insurance plan.

- **HTA Model**

The Health Service Executive (HSE) is responsible for decisions regarding drug pricing and the reimbursement of new drugs. After receiving market authorisation from EMA, drug companies apply for reimbursement from the HSE. The Corporate Pharmaceutical Unit (CPU) within HSE commissions the National Centre of Pharmacoeconomics (NCPE) to assess clinical and cost-effectiveness for drug classes, including new active substances, new indications for already reimbursed drugs, and reassessment of reimbursed drugs that are associated with a high budget impact or uncertain clinical effectiveness. The NCPE adopts a two-step process for the assessment. In the first step, all submissions undergo a preliminary rapid review. Drugs with a high cost relative to comparators or with a net impact on the drugs budget undergo full HTA in the second step [76].

In Ireland, NCPE conducts an assessment for added therapeutic value, cost-effectiveness and budget impact in two steps. There are no fixed timelines for the assessment process, but NCPE attempts to conduct the rapid review within four weeks, whereas the full HTA takes approximately 18 weeks. These timelines do not include the time taken by the applicant to review and respond to the appraisal report, which is approximately five weeks, during which time a clock stop is initiated [76].

After the evidence appraisal, NCPE submits its recommendations regarding reimbursement to the HSE, which is responsible for price negotiations with the applicant based on the recommendations provided by NCPE and HSE Drug group. There is no fixed timeline reported for patient access to reimbursed drugs after the HTA assessment. The time taken by HSE for price negotiation and decision making may vary significantly case-by-case. A survey conducted by the European Federation of Pharmaceutical Industries and Associations, EFPIA, indicated that the time to drug availability in Ireland averages 541 days after receiving market authorisation from EMA [77].

- **Flexibility, Predictability and Transparency**

The HTA outcomes are partially predictable due to the explicit cost-effectiveness threshold. As part of the 2021 agreement between HSE and IPHA, the cost-effectiveness threshold is €45,000/QALY. However, reimbursement is not guaranteed for drugs with an ICER below the threshold, and many drugs that exceed the threshold can still be reimbursed using managed access and risk-sharing agreements if NCPE determines that there is added therapeutic value and unmet clinical need. Several factors may contribute to the reimbursement decision and any conclusion drawn from the ICER is usually supported by the estimate of uncertainty and strength of the evidence [78]. Although it is difficult for sponsors to predict the HTA outcome with certainty, the appraisal process is predictable due to the availability of detailed guidelines for sponsors on the submission and assessment process. Applicants have detailed information available regarding the requirements of submission. There are templates available on the NCPE website for rapid review, budget impact modelling and full HTA submissions. There are also detailed guidelines available on clinical, economic and

budget impact assessment, providing information on the methods and approaches used in the appraisal process[78].

The process flowchart provided on the NCPE website indicates that the detailed appraisal reports are sent to the sponsors for a factual accuracy check. The sponsors can respond to the appraisal report and indicate if there are any factual inaccuracies in the assessment. The NCPE publishes the technical summary of its assessment on its website. However, it may not provide adequate details to make the process completely transparent for other stakeholders, including the public [76].

The HTA outcome is partially flexible, with certain drugs being given conditional approval based on the clinical need. In Ireland, drugs associated with higher treatment costs (usually for serious, complex and chronic conditions) are covered under a High-Tech Drug (HTD)arrangement. These drugs usually have an ICER above €45,000/QALY, thus being considered cost-ineffective after the HTA. The pharmaceutical companies agree on HTD arrangements usually in the form of a managed access protocol or risk-sharing arrangements. These negotiations are usually confidential and guided by the 2021 pricing and supply framework agreement of HSE with the Irish Pharmaceutical Healthcare Association (IPHA) [79].

- **Equity**

For Ireland, "Achieving equity of health or healthcare is a key consideration of decision-makers [78]". Ireland's guidelines for economic evaluation outline multiple ways in which equity can be interpreted, focussing on "need", expenditure, utilisation, access to healthcare, health, and the possible relations between those concepts[78]. The guidelines cite UK societal preferences to reduce inequalities in health, especially inequalities relating to "socio-economic status", and public preferences to improve health for those with dependents or "worse lifetime health prospects" [78]. The guidelines also note with caution the UK public's attributing lower value to "improvements in health for the elderly and ... those perceived to have contributed to their own ill health" [78].

- **Stakeholder engagement**

There is evidence that Ireland engages HTA methods experts, clinicians, academics, patients, service providers, industry, and the general public, though stakeholders are expressly conceptualised as those with "a direct interest in the process and outcomes" of a HTA, so stakeholders are regarded as "distinct from the general public" [80].

- **Special Pathways**

As discussed above, certain high-cost treatments with an ICER above the threshold may be considered cost-ineffective after HTA assessment. But depending upon the clinical need, these drugs can still be reimbursed using managed access and risk-sharing agreements. The academic literature indicates that the criteria used by the NCPE to decide if a full HTA is required are robustness of the clinical data, low budget impact and small population with an unmet clinical need. However, these criteria are not specified on the NCPE website or included in any documentation or guidance used by

applicants, therefore it is not clear how these are weighted in the decision of whether to carry out a full HTA [81].

There is no special pathway for orphan drugs assessment, however a national committee, the HSE Technical Review Committee for Rare Diseases, was established in 2018. This committee is responsible for providing recommendations regarding clinical effectiveness and any other relevant clinical issues that must be considered for the reimbursement of orphan drugs. The committee only meets at the request of the HSE Drug group for advice on a specific submission. The committee includes members from the HSE Rare Disease Programme, consultants with rare disease expertise, pharmacists, health technology assessors, and a representative from the Health Information and Quality Authority (HIQA) [82]. However, it is not clear whether there is a separate pathway for the assessment of orphan drugs.

ITALY

The Italian healthcare system is a national, universal healthcare system, called the Servizio Sanitario Nazionale *(*SSN). It automatically covers all citizens and legal foreign residents. The SSN-covered benefits include pharmaceuticals, inpatient care, outpatient specialist care, preventive medicine, primary care, maternity care and hospice care. It is funded by value-added and corporate tax revenue collected by the national government. The national government collects these tax revenues and allocates them back to regions for health service delivery. Although the national government is responsible for health policies and priorities, the organisation and delivery of health services are essentially decentralised. There are two autonomous provinces and 19 regions responsible for healthcare delivery through 100 local health units. The decentralised and regional structure of healthcare delivery means that the quality of healthcare service may vary across regions. Approximately 10 percent of the population also has some form of supplementary private health insurance for services that are not covered by SSN. There are two types of private health insurance available in Italy: corporate cover provided by employers for employees and their families, and noncorporate cover, where an individual buys cover for themselves and their family [14].

- **HTA Model**

Currently, Italy's HTA system is fragmented and divided into regional and national agencies. At the national level, the Italian medicine agency (AIFA) is responsible for assessment and reimbursement decisions of concerning drugs across all of Italy. Regions such as regions Emilia-Romagna and Veneto also have formal HTA processes, while many others have some form of HTA activity for reimbursement decisions for drugs. Very limited information is available regarding the HTA process, as most documents, reports and guidelines are published in Italian.

AIFA’s pricing and reimbursement negotiation process occurs in the following stages:

1. The market authorisation holder (MAH) submits to AIFA a dossier containing pharmacoeconomic analyses of the proposed drug against a comparator drug/therapy to AIFA. The dossier must be based on the AIFA Guideline, available on the agency's website.
2. The AIFA conducts an initial administrative check for the completeness of the dossier.
3. AIFA's HTA and Pharmaceutical Economy Division, with the help of the secretariat, conduct the critical evaluation of the pharmacoeconomic analyses submitted by the MAH. Literature review may also be conducted to identify any further published studies.
4. During this process, recommendations and decisions taken by other countries for the same drug are also taken into consideration.
5. In the final phase, an economic-financial impact assessment is carried out.
6. The final assessment draft report is then sent to the Scientific Technical Committee (CTS) for the appraisal and final binding decision regarding the added therapeutic value of the drug.
7. The Pricing and Reimbursement Committee (CPR) then conducts price negotiations with the applicant.
8. The outcome of the negotiation process is then referred to the AIFA Management Board for the final decision regarding reimbursement.

In 2017, AIFA published new criteria to determine the innovativeness of drugs. The criteria are based on clinical need, added therapeutic value and the quality of the available evidence base. If a drug is identified as fully innovative then it is immediately included in regional drug formularies, and funded through an innovative drug fund (both for oncology and non-oncology drugs). There is no payback mechanism associated with the approval. The drug can be funded with innovative status for up to 36 months before being reassessed. If a drug is identified as merely conditionally innovative, it is included in regional drug formularies at the price negotiated. Finally, drugs identified as non-innovative are not recommended for reimbursement [83].

As per the EU Transparency Directive (Directive 89/105/EEC), the price and reimbursement decisions are completed within 180 days. However, the time to patient access is variable across different regions in Italy, since some regions may conduct additional assessments of innovation for listing the drug in regional formularies [84]. Some drugs (mainly orphan drugs, drugs for unmet clinical needs and only-hospital-use drugs) are prioritised and assessed through a fast-track process that takes approximately 100 days. To fast-track the market entry of such drugs, AIFA is required to arrange for provision and automatic inclusion into a C-nn class (reimbursement is yet to be negotiated) while waiting for the assessment and price negotiations to be completed. This means that these drugs can be accessed before the market authorisation is granted or a decision on reimbursement is made. During this period, the price of the drug can be set by the MAH and covered entirely by the patient. For

the fast-track process, the reimbursement application to AIFA may be submitted in parallel to the market authorisation or before the market authorisation is issued [84].

- **Flexibility, Predictability, Transparency**

The HTA outcome is partially flexible, since AIFA implements a wide range of approaches to manage budget impact and uncertainty in the cost and clinical effectiveness analyses. Based on the clinical need, some drugs are conditionally approved through managed-entry agreements. These agreements are usually for drugs that have a high level of uncertainty in the evidence base. The agreements can be outcome-based (with risk sharing and payment by results, say) or financial (with cost sharing, volume agreements and capping) [85].

Regarding predictability, no information is available in English on the AIFA website, so information was extracted from the academic literature. There are guidelines available in Italian regarding submission requirements and the type of information required from applicants that will inform the assessment process. However, academic literature indicated that there is no explicit threshold or prespecified value for establishing the clinical and cost-effectiveness of a drug. The price negotiation process is complex and might be influenced by varying economic, social and clinical factors. Economic evaluation was not mandatory for pricing and reimbursement applications, except for orphan drugs. However, after March 2021, updated AIFA guidelines ('Guidelines for the compilation of the pricing and reimbursement application') highlighted that economic evaluation will be integrated into the decision-making process for all drugs, rather than being limited to a specific class. Cost-effectiveness estimates such as ICERs are increasingly being used in the decision-making process, but no explicit threshold for decision making is mentioned in the guidelines [86, 87].

The transparency of HTA outcomes for sponsors and other stakeholders is not clear. No information was found on whether sponsors can participate in the HTA assessment and appraisal process or have access to information on how AIFA committees reached a specific decision. After determining the clinical and cost-effectiveness of the drug, the Price and Reimbursement Committee (CPR) initiate the price negotiation process with the sponsor. However, it is not clear whether the details of the assessment and appraisal process are discussed in the price negotiation process. The list of medicines that received full or conditional reimbursements is published on the AIFA website, along with the assessment report (in Italian). However, it is not clear whether sufficient details are provided in the published reports to make the HTA process transparent for all other stakeholders including the public. Finally, the details of managed entry agreements such as conditions of the agreement or discounts, are confidential.

- **Stakeholder engagement**

There are a few experiences of patient involvement carried out at the national level. (English-language evidence is minimal). There is evidence that "patients are not involved in review processes" [88].

- **Special Pathways**

Although there is no separate assessment pathway for first-in-class or first-in-indication drugs, the innovativeness-based assessment framework introduced in 2017 does ensure easier and faster access to market for innovative drugs. Similarly, under this framework, innovative drugs that meet a high unmet clinical need but are associated with a high budget impact or uncertain evidence can be approved for conditional access, with a view to managing budget impact, addressing uncertainty in clinical or cost-effectiveness, and optimising performance.

Italy follows the EMA definition of orphan drugs. Therefore, drugs so designated by EMA are given priority over other drugs and fast-tracked, reducing the assessment period from 180 days to 100 days. AIFA also ensures early patient access to orphan drugs, specifically for chronic or severe conditions with no alternative therapies, with reimbursement occurring before market authorisation. The inclusion of an orphan drug in a C-nn list is based on a request from patient associations, scientific societies, health facilities, academic institutes, and recommendations from CTS [85].

GERMANY

Health insurance is mandatory in Germany and is provided by two subsystems: statutory health insurance (SHI) comprising nongovernmental, not-for-profit health insurance plans known as sickness funds; and private health insurance. Almost 86% of the population is enrolled in the SHI, which provides coverage for the inpatient setting, the outpatient setting, prescription drugs and mental health services. Both employers and workers contribute to the sickness funds through wage contributions (14.6%) and a supplementary contribution (1.6% of wage). Citizens with an annual pay higher than the wage threshold (EUR 66,600) can opt out of SHI and select private insurance, but the government provides no subsidy for private insurance. The national government is not directly involved in the delivery of healthcare services but has wide-ranging regulatory authority. Under the legal supervision of the Federal Ministry of Health, the Federal Joint Committee determines which services can be covered by sickness funds. The Federal Joint Committee (G-BA) is a public legal entity comprising of the four leading umbrella organisations of the self-governing German healthcare system: the National Associations of Statutory Health Insurance Physicians and Dentists; the German Hospital Federation; and, the Central Federal Association of Health Insurance Funds. These decisions are based on HTA, which is referred to as benefit-risk assessment. All therapeutic products in non-hospital or ambulatory care must receive positive recommendations concerning clinical and cost-effectiveness to get reimbursed by sickness funds [14].

- **HTA Model**

An independent scientific institute, the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG), is

responsible for evaluating the added therapeutic value and cost-effectiveness of drugs [14]. To make a new drug available in the German market, a company needs to first apply for market authorisation, which will allow the company to sell the drug with the coverage provided by the sickness funds. The company can either opt for a national authorisation process, through which they can only market within Germany, or authorisation through EMA to market a drug in some or all countries of the European Economic Area. A drug can receive approval for five years, after which a company can apply for an extension if there are no safety concerns. For the first six months, the company can set the price of the drug, during which time the drug undergoes the HTA process to determine the price that will be covered by the SHI funds [14].

The HTA or benefit assessment is carried out immediately after the drug is launched in Germany. The company needs to submit a detailed dossier within three months of first marketing the drug in Germany to the Federal Joint Committee (G-BA). The G-BA transfers the submitted dossier to the IQWiG for a detailed comparison of the new drug with the established drug (the comparator). The time from submission to determination of the reimbursement price (in case of a positive recommendation) is usually 15 months. The IQWiG takes a maximum of 3 months to carry out the assessment of the submitted evidence and share their recommendation regarding the additional benefit level of the submitted drug. The pharmaceutical company is provided the opportunity to comment on the recommendation and provide any additional evidence. In the next 3 months, the G-BA assesses the IQWiG recommendation and additional evidence submitted by the pharmaceutical company. The G-BA then makes the final decision on the additional benefit. If an added benefit is established, a reimbursement price negotiation is carried out between the company and SHI bodies. The price negotiations must be completed within 6-9 months. Access to the new drugs is available right after it has received market approval, but the company can set the price for the six months.[89] If no clinical benefit is found over the comparator, the drug will be included in a reference price cluster systems along with other medicines with similar therapeutic and/or pharmacological properties.

In Germany, the added therapeutic value is based on clinical effectiveness and usually no cost-effectiveness analyses are performed. However, if the pharmaceutical company and SHI bodies cannot reach agreement during price negotiations, the arbitration board can consider health economic parameters to reach an agreement. However, no thresholds are used for this purpose.

The early benefit assessment is conducted immediately after receiving the market authorisation. The pharmaceutical company can submit a dossier to G-BA no later than the time of first marketing in Germany to determine the extent to which the SHI bodies will reimburse the new drug.

Germany was a part of Parallel EMA/EUnetHTA 21 Joint Scientific Consultation (JSC), which provides non-binding advice to the pharmaceutical company or applicant after feasibility and proof-of-concept studies but before the start of pivotal clinical trials.

This is to improve the quality of evidence submitted for future HTA assessments. The Parallel EMA/EUnetHTA 21 JSC allowed consultation between HTA agencies and pharmaceutical companies at an early stage in the evidence development process, thus allowing better integration of the different requirements for clinical and economic evidence generation.

In Germany, all drugs are considered reimbursable after receiving market authorisation, unless it is included in the negative reimbursement list (non-prescription drugs and lifestyle medications). After evaluation by the IQWiG, the G-BA can recommend placing drugs on a "negative" list indicating that these drugs will not be reimbursed by the sickness funds [90]. Moreover, all drugs are also subjected to statutory re-assessment resulting in changes in reimbursement status.

- **Flexibility, Predictability and Transparency**

Overall, the German HTA process is not flexible, with specific timelines and strict criteria to determine whether a drug has additional therapeutic benefit over the appropriate comparator. The process follows a hierarchical stepwise approach. When the evidence does not support an added benefit, the outcome is "No added benefit proven".

Pharmaceutical companies can request a consultation by submitting the evidence dossier to the G-BA in advance to get advice on its contents. The G-BA can provide written feedback to the company regarding which additional documents or information must be submitted. Although the approach or method used for assessment is partially predictable, an applicant is not able to predict with certainty what characteristics of the evidence (such as equity considerations, uncertainty in the magnitude of the effect and applicability) influence the determination of any added clinical benefit by the committee and involved stakeholders.

Modules 1-4 of the dossier submitted by the company (including the executive summary, information on the drug and the indication, description of the comparator, and a review of the added benefit) is published in German on the G-BA website. Module 5 of the dossier (comprising clinical evidence like study reports, the regulatory submission dossier, EMA reports, and published and unpublished data) may be published with confidential information redacted. Sponsors are allowed to submit written and verbal statements [91]. The assessment reports are publicly available on IQWiG and G-BA websites three months after the assessment was commissioned, along with comments received from different stakeholders [92].

- **Equity**

Germany emphasises patient voices and equal access to health care for all [93]. Its methods guidance for cost-benefit analysis evinces regard for equity, how the use of QALYs can be problematic and how "greater weight" might be given to "distributional aspects" in economic evaluation[94]. On the second point, researchers report that

"though IQWiG [German] guidance states that QALYs may be used in analysis, in practice they have never been used" [95].

- **Stakeholder Engagement**

Germany engages patient groups and representatives to improve and share information in its HTA [96]. Specifically, an external contractor conducts focus groups and interviews [96]. Five patients are also invited to test some texts for their content and readability [96] Reports are "made accessible to the public"[94, 96] and a "public comment procedure" follows[94].

Germany appears to have "legal norms" that govern who is "entitled to comment" on a given HTA[97]. Applying these norms, the Federal Joint Committee decides "the group of organisations entitled to make statements", and these can include umbrella organisations, manufacturers and scientific and clinical societies [97].

Research suggests that in Germany emphasis is placed on consulting affected persons themselves rather than solely representatives:

> The involvement of affected persons at IQWiG primarily takes place during the initial work on a report within the framework of patient-relevant outcomes and relevant subgroups. Moreover, involvement can also include partaking in hearings. Affected persons include in particular patients (represented by parents or relatives, when appropriate) as well as potential participants in prevention measures. Affected persons are found via the patient representation of the Federal Joint Committee, as well as national or local self-help organisations or groups, hospitals or medical practices, external experts or other routes. The involvement can consist of a personal consultation or providing information in writing (through questionnaires or reports on personal experience), in both cases with documenting potential conflicts of interest [98].

The below table summarises stakeholder engagement in Germany from review conducted by University of Southern California Schaeffer and The Aspen Institute [7].

Table 79 Stakeholder engagement in Germany [7]

Stakeholder Engagement	HTA Committee Representation	Patient Involvement	Appeals	Transparency
- Manufacturers submit dossier for assessment; medical experts and patients are regularly consulted for the assessment - In all important phases of report preparation, the law obliges IQWiG to provide	Main committee: 2 Hospital Federation reps 5 Statutory Health Insurance (SHI) reps 2 SHI physicians 1 SHI dentists 2 impartial members Non-voting participants include patient	Patients or patient reps are asked to review certain text drafts as part of quality assurance Patients are allowed to comment on all feature articles, fact sheets, and research summary drafts	G-BA appeals are part of the price negotiation process No IQWIG appeals process has been identified	- IQWIG results and supplementary information available on their website - Stakeholder comments are published - Data submitted that cannot be published cannot

opportunity for stakeholder comment - External experts are awarded research commissions or advise IQWiG on medical or other topic-related research questions	reps, government reps, and reps from the German Medical Association, German Nurses Association, and Private Health Insurance Providers Federation	be considered in assessments - All experts must disclose COI - IQWiG produces information for a variety of audiences

- **Special Pathways**

There is no special pathway for high-cost drugs, however the price negotiation process that follows the G-BA decision on the added benefit allows SHI bodies and companies to negotiate different arrangements, such as discounts and rebates to lower drug prices for SHI bodies.

In Germany, all advanced therapeutic medicinal products (ATMPs) that have been granted market authorisation need to undergo a benefit assessment process, as other medicines (Arzneimittelmarktneuordnungsgesetz (AMNOG) §35a SGB V Paragraph 1b). However, the G-BA categorises the ATMP as either a medicine or a medical procedure. If the ATMP has pharmacologic properties and its clinical outcome is not dependent on the healthcare professional's skills, it is categorised as a medicine and undergoes the benefit assessment procedure. However, if the administration of the therapy or the skills required for administration are considered complex and essential for the treatment effect, then the ATMP is designated a medical procedure without the need to undergo the benefit assessment process. Such ATMPs are normally assessed by the PEI (Paul-Ehrlich-Institut) [99]. The applicants can ask for G-BA and PEI advice on categorisation before submission.

Many approved ATMPs are also designated as orphan drugs due to small patient population sizes. These drugs often receive market authorisation through accelerated pathways, thus only limited evidence is available for determining their long-term impact. To reduce the clinical uncertainty in the evidence base due to the limited long-term efficacy and safety data, a fixed term can be set by G-BA for a reassessment, usually 1-3 years for any additional clinical evidence [88].

For co-dependent technology, joint reimbursement decision making came into effect on 1 July 2019. The Gesetz zur Stärkung der Arzneimittelversorgung (AMVSG) law laid the foundation for parallel decision making for reimbursement of a companion diagnostic technology (CDx) along with the novel drug. The Institut des Bewertungsausschusses is responsible for informing the G-BA if any adjustments need to be made in the EBM (Einheitlicher Bewertungsmassstab – catalogue for reimbursed services in the public outpatient sector) and facilitates the decision making of the reimbursement of CDx if the medicine is getting reimbursed. The medical device manufacturers and national associations of invitro diagnostic technologies can submit applications for

reimbursement of CDx. The internal working group within the Institut des Bewertungsausschusses will conduct an assessment and appraisal of the application and makes the final decision regarding reimbursement. This process must be completed within 24 months, with 6 months' extension being possible to include the CDx into the EBM [100].

JAPAN

Japan's statutory health insurance system (SNHI) provides universal health care. It is funded through taxation and individual contributions, and covers 98.3% of the population [14, 101, 102]. A Public Social Assistance Program covers the remaining 1.7% of the population. Over 70% of the population utilises supplemental private coverage [14]. Japan has a pooled, multi-payer system. No HTA was required for medicines to be listed in its National Health Insurance (NHI) before 2016, with listing being based solely on the outcome of the price negotiation between sponsors and the government. If sponsors satisfied the price set by the government, the product could be listed. The price of a new medicine was set by comparison with similar products on the NHI list [101]. Similar medicines could be defined by the indication, mechanism of action, molecular formula, and route of administration [101]. The price could be adjusted according to the level of innovation, clinical benefit, marketability, use in children, and so on. This adjustment was considered in terms of a price "premium", making the new drug more expensive than the comparator.

Japan's HTA program (comprising cost-effective analysis) was implemented in 2019 [102]. Unlike other countries, Japan uses HTA only for price adjustment, not to determine reimbursement status. Thus, the HTA is conducted after listing for already reimbursed medicines. The HTA assessment is conducted by independent specialist organisations and the HTA report is appraised by the Chuikyo Cost-benefit Assessment Specialist Committee [102]. The HTA is proactive, with the Central Social Insurance Medical Council (CSIMC) choosing the topic and making the final decision on price [102].

- **HTA pathways**

Sponsors need to submit a cost-effectiveness analysis related to the target medicine (selected by CSIMC) based on the analytical framework agreed on after consulting with the first expert committee. After the sponsor finishes the analysis, the second expert committee confirms the analysis after an academic analysis occurs to validate the sponsor's submissions. The third expert committee validates the final analysis and gives approval. Then CSIMC can give final approval of the whole evaluation. In this way the new price of the medicine is determined.

After market authorisation, it takes only 66 days to initiate the reimbursement process [101]. It takes nine months for the sponsor analysis, including preliminary consultation to set the analytical framework, first expert committee validation, and second expert committee validation. It takes a further three or six months for the academic analysis,

and three months for final approval of the new price (the third expert committee validation and CSIMC approval). In total, this equates to 15 to 18 months to reach the HTA recommendation.

There was no report on alignment between the regulatory process and reimbursement. The whole HTA process is for disinvestment.

- **Flexibility, predictability and transparency of HTA pathways**

The HTA outcome does not indicate reimbursement status but instead the price adjustment needed for the already reimbursed product. Therefore, the HTA outcomes are flexible. There is no report detailing HTA working schedules; it is only known that the topic selection for HTA happens four times per year. There is a guideline for cost-effectiveness evaluation, including different steps of the HTA process [103], and the method for assessment is available [104]. The HTA evaluation steps are predictable. The method of calculating the needed price reduction is transparent [103], given the price that comprises the HTA outcome. In all, the predictability of the HTA appraisal process is partial. Sponsors can consult on the assessment by contacting the National Institute of Public Health; therefore, the HTA process is transparent to sponsors. The HTA process is transparent to the public, the public can access the company submissions and the final HTA report. However, the price sections are redacted.

- **HTA pathways for specific technologies and populations**

In Japan, HTA is only for medicines that have a large influence on public health insurance finance[103]. These could be newly or previously listed products with high peak sales or a high unit price, and they are allocated to five groups according to these features (classes H1-H5). Product prices are set according to reference products, which can also come in for HTA [103]. CSIMC selects drugs for HTA four times per year, and only drugs in class H1, H3 or H4 experience immediate HTA after selection [103].

Japan has some special pathways for medicines to treat rare diseases, cancers and paediatric indications. If the medicines are solely used for rare diseases or children, the HTA can be waived, meaning that there will not be any price adjustment once the medicine is reimbursed. If the medicines can treat, but are not limited to treating, rare or paediatric diseases, or if the medicines are used for cancer treatment, then they may still be subjected to HTA but will receive special consideration in the appraisal process and price adjustments.

- **Equity**

Japan believes that “equity considerations are important”, though it states that fuller consideration of “Ethical and social issues should be discussed in the future”, with a suggestion that they are integral to HTA's “appraisal” phase (i.e., decision making) but not to “assessment” [105]. Japan gives special consideration to cancer, conditions with “insufficient treatment” options, and “rare, paediatric, and severe diseases” [103]. Specifically, Japan “raises the cost per QALY thresholds for drugs with paediatric indications” [95].

- **Stakeholder engagement**

Japan receives industry submissions then consults with industry and cooperates with academics [106]. One committee includes "6 members from the public interest" (though academics are offered as an example), alongside many more clinicians [103]. Japan states that economic findings should be "made public" [105]. One report found that "in practice stakeholder engagement and transparency are lacking" in Japan and that the country flatly "does not have patient involvement" [7].

The below table summarises stakeholder engagement in Japan and is copied from [7].

Stakeholder engagement	HTA committee representation	Patient involvement	Appeals	Transparency
Manufacturers submit data at start of appraisal process; otherwise unclear how stakeholders are engaged but said to be "insufficient"[42]	Organisation includes 6 insurer reps, 6 provider reps, and 4 public interest reps Non-voting members include 4 manufacturer reps and 3 health economists	None	Manufacturers can appeal if they disagree with price, but unclear how appeals have been implemented in practice	None

NORWAY

The Norwegian healthcare system is semi-decentralised with the national government responsible for regulating, funding and supervising the provision of care services. The national government is also responsible for hospitals and specialty care but these are managed through regional authorities. Primary and preventive care is the responsibility of municipalities in collaboration with the local counties. All residents get automatic health coverage, which is funded by two main sources: general taxation (national, county and municipal tax revenues) and the national insurance system. National taxation funds 76% of the health care services. The national health insurance scheme funds 10% and is financed through insurance contributions from payroll (40%), members (2%) and national taxes (28%) [14].

- **HTA Model**

In Norway, HTA is conducted in three forms: mini-HTA, STA and full HTA. The mini-HTAs are conducted within hospital units and limited to hospital-based interventions. The STAs focus on a single health technology and are performed by the Norwegian Medicines Agency (NoMA) and the Norwegian Institute of Public Health (NIPH) (which handles non-medicines). Full HTAs or multiple technologies assessments (MTAs) may be used to compare various technologies that have been in clinical practice. Those assessments are performed at the national level by the NIPH [107].

All new drugs with market authorisation need to undergo STA before they can be publicly funded by the national health insurance scheme (folketrygden) or by the regional authorities for use in specialist care (Nye metoder). The market authorisation holders submit a complete dossier comprising of clinical and cost-effectiveness analysis and budget impact of the submitted drug. The NoMA is responsible for the assessment of the submitted dossier and provides recommendations to Procurement Services Ltd (Sykehusinnkjøp HF) for potential price negotiations with the MAH. The outcomes of the price negotiations and the HTA recommendations are then forwarded to the Decision forum, which takes the final decision regarding reimbursement.

NoMA also maps new active substances or extensions of therapeutic indications through horizon scanning 6-12 months before market authorisation. The purpose is to prioritise new and important drugs for HTA. The horizon scanning process also helps to determine the level of assessment required in the HTA step [108].

Upon receiving market authorisation, the MA holder needs to apply to NoMA for the maximum price. The maximum price is decided using a reference price system, which takes into consideration the lowest prices from 9 selected European countries. Patients can access the drug right after the market authorisation, however, it is not reimbursed, and the maximum price is paid by patients through out-of-pocket payments.

Norway is also part of the Nordic collaboration, FINOSE, for joint assessment. FINOSE offers transparent and efficient evaluations of drugs for reimbursement in four countries: Denmark, Finland, Norway and Sweden. In the FINOSE assessment, sponsors make identical submissions to respective agencies of the member countries along with any other country-specific submissions agreed upon in the pre-submission meetings. The four agencies carry out joint assessments, collaborating and sharing of material between agencies. The agencies produce a joint draft report which informs the price negotiations and decision-making at the national or Nordic level [109].

NoMA aims to complete its assessment within 180 days of submission of the dossier. However, if further information is required from the sponsor, a clock-stop is initiated which can delay the assessment process. There are three reimbursement categories: Schedule 2 (general reimbursement class) covers drugs on the reimbursement list for a specific diagnosis that requires long-term treatment (at least months of medication per year). These drugs undergo HTA with pre-specified criteria: health benefit, resource use and severity. From 1 January 2023, the reimbursement rate is 50%. Under Schedule 3, reimbursement is granted on an individual basis and by submission from a physician. The treatment must last more than 3 months, and the patient must be different from the patient group assessed for Schedule 2. Schedule 4 covers medicines to treat serious contagious diseases and the reimbursement rate is 100% [110].

In 2016, the Norwegian government proposed a set of principles for priority setting to promote fair access. In line with these principles, some drugs for severe conditions with high unmet clinical needs can be prioritised for assessment based on horizon scanning

reports and granted pre-approved reimbursement if the relation between patient benefits and resources is reasonable.

Norway has no direct process for disinvestment of obsolete or low-value drugs, however, it uses a tiered price system for non-patented medicines. When the drug patent expires and there are biosimilars or generic drugs available for the same indication, the price of the drug is reduced in a stepwise fashion with a fixed cut rate. The tiered price is set as a percentage of the maximum pharmacy purchase price (PPP) of the drug at the time the generic competition occurs. The price is cut by two steps (for synthetic drugs) or three steps (for biological drugs) [111].

- **Predictability, Flexibility and Transparency**

There is no flexibility in the HTA appraisal process in Norway, since most of the decision making is limited to reimbursement or no-reimbursement. Conditional approvals and risk-sharing agreements are not common for outpatient drugs.

The HTA process is predictable, since the guidelines for assessment are available online. These detail clinical effectiveness evaluation, economic evaluation, QALY estimation, sensitivity analysis, and other factors that may influence reimbursement. The express purpose of these guidelines is to ensure that all drugs are consistently appraised using the same criteria.

Following completion of the HTA, the HTA report and the recommendations provided by the commissioned agency are sent to the sponsor for input. This makes the assessment transparent for sponsors. The assessment reports are publicly available, however information on price negotiation and commercial or academic-in-confidence information is redacted.

- **Equity**

In general, Norway examines “absolute shortfall” as an index of severity. Norway is mindful not to define very small patient groups with rare conditions too broadly, since doing so in creating a special HTA pathway “will undermine the objectives of equitable and fair priority setting” [112].

- **Stakeholder engagement**

Norway engages industry and subject experts on HTA methods. It makes reports public, after giving industry opportunity to can note whether the reports contain confidential information [109].

- **Special Pathways**

There are no specific pathways for high-cost drugs and drugs focusing on unmet clinical needs. However, Norway’s priority setting criteria do give priority to drugs for more severe conditions or unmet clinical needs, even if resource usage is high.

Antibiotics are currently not reimbursed due to the criterion of reimbursement being limited to a long-term treatment (of at least 3 months). For rare diseases, orphan drugs

may not meet the criterion of resource use being reasonable proportional to benefits. However, the third paragraph of the Norwegian Regulations on Medicinal Products §14-5 states that where drugs cannot satisfy these conditions (specifically drugs for very small patient groups with extremely severe conditions) resource use must be assessed in light of any large expected benefit for patients. The HTA process has been adapted to consider a greater willingness to pay for orphan drugs. The criteria for any drug to be considered under the third paragraph (Section 14-5) are as follows. The drug must target a very small population. There must be fewer than approximately 1 patient per 100,000 people or fewer than approximately 50 patients in Norway. The condition must be extremely severe, with severity measured as absolute shortfall, which must be at least 30 good life years. Finally, treatment must provide considerable clinical benefit, with a minimum of two good life years gained compared to the standard treatment [112].

POLAND

Poland's healthcare system is based on a social health insurance known as the National Health Fund, which is mandatory for all residents. The system is centralised, with the national government (the Ministry of Health) being responsible for the planning and governance of health services. The national government shares some of these responsibilities with three administrative levels. The big hospitals are owned by regional governments, whereas specialist clinics and smaller county hospitals are owned by local counties. Primary care practices are owned by municipalities, though most of these practices are private. The National Health Fund is funded by health insurance contributions and the state budget. The level of health insurance contributions is determined by law and amounts to 9% of a person's salary. Private health expenditures include voluntary health insurance and out-of-pocket payments. Voluntary health insurance comprises health service packages usually provided by employers and supplementary health insurance provided by private companies. There is a low level of financial coverage for outpatient medicines which account for most out-of-pocket spending [113]. Outpatient medications are available for a partial payment or a lump sum.

- **HTA Model**

Medicines are included on the reimbursed medicine list through HTA performed by the Agency for Health Technology Assessment and Tariff System (AOTMiT). Applications for reimbursement (or setting or modifying the ex-factory price) are submitted by the MAH to the Ministry of Health. AOTMiT is commissioned by the Ministry of Health to assess the submitted clinical, economic and budget impact analyses and to provide recommendations regarding reimbursement. The HTA report is appraised by the Transparency Council, then AOTMiT provides its final recommendation on reimbursement based on the report and any applicant remarks. The Minister of Health, after receiving the recommendations from AOTMiT and the Transparency Council,

makes the final decision. Finally, the Economic Commission conducts price negotiations with the MAH before listing the medicine on the reimbursement list.

Under the Reimbursement Act, the Ministry of Health can set up limit groups for different reimbursed drugs. In a specific drug limit group, a funding limit is based on the highest wholesale price of a drug among the lowest wholesale prices per daily dose. If the sales price of a drug is higher than the financing limit of a group, the difference between the base limit and sales price is covered by patients as an out-of-pocket payment [114].

AOTMiT sends its recommendations to the Transparency Council within 60 days of receiving an application. However, if further information is required from the sponsor due to an incomplete application, AOTMiT can ask the sponsor to provide supplementary information within 21 days. During this time, a clock stop is initiated. There is no information available on how long it takes for price negotiations to occur and for patients to access the reimbursed drug. However, as per the transparency directive of the EU, the reimbursement and pricing decision process must be completed within 180 days [115].

AOTMiT's recommendations are published on its website for public consultation. However, it is not clear whether sufficient information is provided regarding the evidence and reasoning behind recommendations to make the process completely transparent for the public and other stakeholders.

- **Stakeholder engagement**

There is evidence of a "lack of comprehensive stakeholder involvement" in health system planning in Poland [116]. Consequently pilot projects have been "difficult to implement … because they did not reflect the realities on the ground", with the imputation that stakeholder engagement could have helped to prevent this [113]. In Polish HTA, applications are "submitted to the Ministry of Health by a representative of the marketing authorisation holder for the health technology" (presumably this typically refers to industry). Expert opinion is solicited in assessing applications, and the applications along with their assessments are made available to the public, who may provide comment within seven days [117].

SINGAPORE

Singapore has a multi-payer system, where the care services are funded through combination of government subsidies, risk-pooling through both mandatory government health insurance plans and voluntary private health insurance plan (MediShieldLife), compulsory individual health care saving accounts (Medisave), a government endowment fund (MediFund) and out-of-pocket contributions from patients. MediShield Life is mandatory health insurance for all citizens and permanent residents, providing lifelong cover for hospital bills and some outpatient treatments. MediSave helps with out-of-pocket payments, with contributions coming from 8-10% of

an individual's salary. MediFund is the government safety net that helps cover the out-of-pocket costs that MediSave cannot reimburse for needy Singaporeans [14]. People also have options of choosing private health care. The Agency for Care and Effectiveness (ACE) is the national HTA agency, responsible for generating HTA reports. The reports are considered by the Ministry of Health's (MOH) Drug Advisory Committee (DAC), which makes final recommendations[118]. Topics for HTA come from healthcare professionals from public healthcare institutions, sponsors and literature searches and horizon scanning conducted by an ACE technical team. A sponsor can only submit a topic if it is relevant to a new medicine or indication [119]. The same drug with a new formulation or strength cannot be submitted by the sponsor; this can only be put forward by a public healthcare institution as part of an annual topic program [119].

- **HTA pathways**

The timelines of the HTA process mainly differ according to the clinical claim made in the submission (non-inferiority versus superiority/inferiority). The former is mainly evaluated under an expedited pathway, whereas the latter is given a full evaluation. A stakeholder workshop may be held to discuss the scope of a full evaluation[118].

For non-company submissions, it takes 2-3 months to generate an expedited HTA report and 6-9 months for a full evaluation. For company submissions, it takes 20 weeks for both expedited and full evaluation [119].

Prioritisation occurs for topic selection. In the annual call for topics, ACE will filter and score topics based on the therapeutic gap, clinical need, disease severity, population size, comparative effectiveness and safety, cost-effectiveness and resource impact. Topics with high scores are likely to be evaluated [118].

The alignment between the regulatory and reimbursement process is partial because entering the parallel process depends on sponsors [119]. For example, for cancer medicine submissions, HTA may start right after the MA application.

After ACE's evaluation, if the existing medicine on the Standard Drug List (*SDL*) or Medication Assistance Fund (*MAF*) offers no additional therapeutic value over other medicines within the same class or is not considered cost-effective, it may be delisted or recommended to be replaced with other me-too drugs. Delisted medicines are not considered for re-listing at least for 3 years. In some cases, DAC may also recommend delisting of a reference biologic or replacing it with another biosimilar.

- **Flexibility, predictability and transparency of HTA pathways**

The HTA decision is to either 'recommend' or 'not recommend'. Decisions are made based on a matrix of factors, with consideration to the clinical benefits of a technology to the comparator (whether similar or greater), clinical need, and the cost of the technology (whether similar, lower, or higher). . In case of uncertainties regarding clinical effectiveness, cost effectiveness and budget impact of the technology, a risk-sharing arrangement can be proposed by the sponsor during price negotiations that typically occur in parallel to the HTA evaluations..

The DAC meeting is held three times per year, though additional meetings may be called by the Chairman, where necessary. The HTA evaluation steps are not flexible. The steps of each HTA process are clear to sponsors and need to be performed in a fixed timeframe. In the guideline, the matrix of factors relevant to the decision is available, but how these factors contribute to the HTA decision is unknown. No ICER threshold is specified. Sponsors are unable to predict the HTA outcome. The methods used are clear, including in literature review, clinical evaluation, and economic modelling. Therefore, the HTA evaluation steps are predictable.

The HTA process is transparent to sponsors, who can participate by addressing points of clarification. A very brief HTA report summary is published for each medicine as a form of guidance [120], that does not contain any confidential information.

- **Equity**

Singapore aims to fund medicines "in an equitable, efficient and sustainable manner" and special consideration can be given to "unmet clinical need or equity considerations" [119].

- **Stakeholder engagement**

Singaporean HTA works closely with patients and clinicians, while negotiating prices with industry and seeking expert views [121], including from academics [119]. Mention is made of engaging the public and promoting public understanding of HTA, though "consumer" is the overarching term [119]. There is a dedicated Consumer Engagement and Education team [119] and a published guide that details the patient involvement process and methods used [122]. The guide describes "the contribution that patients and their carers can make … [to HTA] and healthcare decision-making in Singapore by providing their experiential knowledge of different medical conditions and health technologies, and explaining which outcomes are most important to them" [122].

- **HTA pathways for specific technologies and populations**

[119]Risk-sharing arrangements (RSAs) address uncertainties surrounding the reimbursement of a technology [119]. RSAs are most commonly implemented with cancer drugs in the form of price volume arrangements (PVAs) over a 5 year period to manage uncertainties in the budget impact of the drug. Technologies with higher budget impact may require additional approval before they can be recommended for reimbursement. All RSAs are deliberated upon by the DAC, who may also recommend for the renewal or extension of existing RSAs if for example, underlying uncertainties persist..

In Singapore, there is no special HTA pathway for assessment of medicines treating rare diseases, however there is a the rare disease fund (RDF) for providing long-term financial support for patients with rare diseases requiring treatment with high-cost medicines [118]. It is funded through government and community donations and overseen by Kandang Kerbau Women's and Children's Hospital [118]. Patients can access the medicines listed on the RDF by sending a request through medical social workers in

their public healthcare sector. The eligibility for funding of each individual request is assessed by the RDF Committee.

A medicine should meet the following criteria to be considered for listing in the RDF [118]: 1) It should have market authorisation from the Health Sciences Authority (local regulatory), FDA, or EMA; 2) Medicine must be developed for treating a rare but clinically defined genetic condition that is life-threatening and chronically debilitating (defined as prevalence of less than 4 patients per 10,000 population); 3) evidence indicates that medicine is likely to substantially extend a patient's lifespan and improve their quality of life; 4) there is no cheaper alternative (including non-drug therapy); 5) medicine is not indicated for other conditions, except for other rare conditions; 6) the annual cost of medicine has a significant financial burden on the patient and/or their family or carer.

Medicines for rare indications can be nominated by annual topic submissions, clinicians (treating patients with rare disease)/local public health sectors. After the topic is selected, ACE prepares a clinical briefing document with the help of the Rare Disease Expert Working Group (RDEG). RDEG comprises of a range of clinical experts in rare diseases, providing information such as local epidemiology profile of indications, current clinical practice and potential future clinical algorithms, and evaluation of eligibility of medicines to be listed in RDF. Clinical briefing document also includes price information and funding outcomes from reference overseas jurisdictions, such as Australia, New Zealand, UK, South Korea, and Taiwan, where available. Clinical briefing document and RDEG recommendations form the basis of final decision [118].

The final decision is made by voluntary RDF Committee comprising of community representatives, who are also responsible for supporting fundraising efforts for the RDF. After the decision is made, ALPS Pte Ltd. [123], which is a public healthcare supply chain agency, is responsible for supply negotiations (prices based on ACE briefing document) and establishing procurement arrangements. RDF Committee might change the decision if there is any change to the price of a medicine after it has been recommended for inclusion in the RDF. In this case, ACE would contact sponsors to resubmit pricing proposals and thus be re-considered by RDF Committee [118].

SOUTH KOREA

The healthcare system in South Korea is two-tiered, with the National Health Insurance (NHI) and Medical Aid. Most of the population is covered by the NHI, while low-income earners are covered by Medical Aid [124]. The NHI is majorly funded by the beneficiaries premium (including both paid by employers and individuals) and government subsidies [125].

The NHI provides a benefits package for different services, such as emergency care, diagnosis, treatment, medicines, traditional medical care, and dental care. Co-payments range from 30-60% for outpatient services, whereas hospital care incurs a 20% co-

payment. Due to the high co-payment, 90% of the population has a private health insurance plan. By contrast, Medical Aid covers both insurance premiums and co-payments, being a government subsidy program to aid low-income earners with healthcare services.

The National Evidence-based Healthcare Collaborating Agency (NECA) is a representative HTA agency in South Korea but only conducts HTA for medical services under the Medical Act. HTA for pharmaceutical products is conducted by the Health Insurance Review and Assessment Service (HIRA)[126].

The Assessment Committee within the HIRA conducts the HTA, with a focus on the comparative effectiveness and cost-effectiveness of the medicine[127]. The Pharmaceutical Benefit Coverage Assessment Committee (PBCAC) conducts the HTA appraisal and makes recommendations [127].

PBCAC comprises a range of specialists, such as clinicians, statisticians, health economists, and representatives from patient advocacy groups [127]. Recommendations are delivered to the Minister of Health and Welfare (MoHW) so the medicine can be listed [127]. HTA is conducted on a hybrid model. Sponsors of new medical technologies can submit evidence dossiers to the Minister or the president of HIRA for healthcare benefit coverage determination [128]. The Minister can also determine and announce the eligibility of healthcare coverage based on the results of review committees, even without a prior application for healthcare coverage [128].

- **HTA pathways**

HIRA's review takes 150 days for the initial assessment and 120 days for reassessment [126]. So a total of 270 days would elapse from receipt of the application to the decision made by the Minister [126].

No report was found on reimbursement before market authorisation.

There are many prioritisation pathways for medicines with Managed-Entry Agreements (MEAs) [129-131]. When an MEA is implemented, the medicine is reviewed after four years to determine whether the MEA should be extended. Sponsors may be required to pay back monies to the NHI if pre-specified criteria are not met.

- **Flexibility, predictability and transparency of HTA pathways**

No report was found detailing the HTA evaluation steps, so it is unknown whether the HTA process is flexible, transparent or predictable.

- **HTA pathways for specific technologies and populations**

Korea's pathways for new medicines that achieve reimbursement listing are highly flexible, mainly differing when it comes to price calculation and negotiation. The price negotiation process can be waived for a medicine with alternatives if the sponsor accepts the set discount rate based on the weighted average price determined by the market share of alternative medicine based on NHI reimbursement claim data [131]. For a

medicine without alternatives, there are distinct reimbursement pathways involving (1) essential medicines, (2) a risk-sharing agreement (RSA), and (3) pharmacoeconomic evaluation exemption [131].

If a medicine is designated as an essential medicine, then cost-effectiveness evaluation can be waived and the price is set according to the price listed in reference countries (UK, Italy, France, Germany, Switzerland, the US, and Japan). RSAs are used for medicines that (a) are anti-cancer agents or orphan medicines for rare diseases, (b) lack an equivalent or alternative, and (c) treat serious, life-threatening conditions. The medicine review committee can also conclude that further agreement on additional conditions is necessary after considering the severity of the disease, social influences, and other influences on public health. RSAs can last four years; re-evaluation is needed to maintain the listing status. There are four types of RSA. The first is a medicine performance-based money-back guarantee. If the pre-set goal of a particular treatment effect is met, then the listing can be maintained. Otherwise, the sponsor is required to refund the full cost of the medicine to NHI. Second is an expenditure cap, where the sponsor is required to pay back whatever exceeds the NHI's pre-set annual expenditure. Third is where a sponsor refunds a particular percentage of the nominal price to NHI. Finally, there is a utilisation cap or fixed cost per patient [129]. Pharmacoeconomic evaluation exemption helps with the listing of medicines that do not meet the criteria for an RSA. Economic evaluation can be waived for a medicine without alternatives if (1) it treats a serious, life-threatening condition, (2) the number of patients is too small to generate evidence, and (3) the medicine is reimbursed in at least three of the seven reference countries. For medicines under this scheme, risk is shared with NHI via an expenditure cap [129].

- **Equity**

Some "ethical considerations ... such as "vulnerability" are embedded" in Korean HTA decision making, but "there is no information available" concerning the concepts or how to apply them in decision making [132]. Some scholars has critiqued Korean funding decisions on oncology drugs for there being "no discussion about fairness", and more generally scholars have argued that equity is "not clearly defined" and "rarely observable" in Korean HTA decision making [133].

- **Stakeholder engagement**

In Korea, the funding decision is made by the Medical Procedure Expert Evaluation Committee, which consists of 22 stakeholders "randomly selected from the pool" of 326 expert groups, encompassing "health authorities, medical specialty societies, patient advocacy groups, [and] academia", with appeals sometimes being made by, for example, "clinicians and healthcare providers" [134]. Korean regulations ensure that manufacturers can "voice their opinions during the reimbursement process" [135]. A Citizen Committee for Participation was formed to make recommendations for 45 medical services, though this appears to have been something of a pilot programme [135].

SPAIN

The Spanish National Health System (Sistema Nacional de Salud; SNS) is based on principles of universal and free access to healthcare services covering 99% of the population. The health system is highly decentralised with administration managed at national and regional levels. The regional level is devolved into 17 autonomous regions. The Ministry of Health under the national government is responsible for the planning and regulation of health services and the health budget, whereas resource allocation, local planning and administration, and the purchasing and provision of health services lie with regional authorities. The SNS interterritorial council, comprising the national health minister and their 17 regional counterparts, is responsible for the coordination of actions and policies across different regions [136].

The SNS is funded through general taxation, with up to 94% of its funding comprising public resources. The benefits package is divided in two. First, there is a common package, which in turn funds a core package, a supplementary package and accessory services. The common package is the same for all 17 regions. Second, there is a complementary package, whereby regions are free to decide which services and products to pay for through a regional fund. Pharmaceuticals and some supplementary services (such as ortho-prosthetic devices) are funded under common package's supplementary package and are subject to patient co-payments.

The Spanish tax system is highly decentralised, with responsibility for tax collection being shared between the Spanish Fiscal Revenue Agency and regional authorities. This applies to both direct taxes (on income and wealth) and indirect taxes (value-added tax). Regional authorities are also responsible for collecting regional taxes (e.g., inheritance and wealth transfer taxes). Due to their shared responsibility for revenue collection, along with independent regional revenue, regional authorities have significant fiscal autonomy when it comes to financing healthcare services. There is also a complex compensation fund to reduce funding imbalance across different regions.

While the provision of healthcare services is mostly decentralised to 17 regions, decisions on new-drug pricing and reimbursement are made centrally by the Interministerial Committee on Pricing of Medicines and Healthcare Products (CIPM). CIPM members span the ministries of Health, Finance and Industry, plus there are three regional members nominated on a rotating basis. Regions are legally required to ensure access to drugs centrally approved for reimbursement, though some regions may establish additional criteria, guidelines and incentives to monitor the use of drugs, especially drugs with a high clinical impact or budget impact [136].

- **HTA Model**

In 2020, the Spanish Network for the Evaluation of Medicines in the National Health System (REvalMed NHS) was established to assess the safety, quality and efficacy of new drugs. It consists of: (1) the Spanish Agency of Medicines and Sanitary Products (La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) for evaluating

added therapeutic value; (2) the General Directorate for Common Portfolio of the NHS and Pharmacy Services (DGCCSF) for conducting economic evaluation; and (3) three members from autonomous regions (nominated on a rotating basis). The regions can also appoint "expert reviewers", organised into seven therapeutic nodes, who are entitled to review the assessment report and provide feedback. The network is supported by a coordinating group representing the parties involved in the REvalMed NHS. The assessment reports (called Therapeutic Positioning Report (TPRs)) are based on a clinical assessment of relative clinical efficacy and safety conducted by AEMPS, economic evaluation conducted by DGCCSF, and input from regional authorities.

The REvalMed NHS assessment process comprises three phases. First, the TPR is sent for consultation to stakeholders, such as patient representatives and scientific societies. The clinical and pharmacoeconomic expert teams update the TPR based on the feedback received. Second, the REvalMed NHS reviewers' group (i.e., the evaluation node) appraises the TPR then the coordinating group publishes it. Finally, the TPR is discussed during the monthly meetings of REvalMed NHS. Based on the assessment and comments received from stakeholders, the committee members draft recommendations. After establishing the drug's additional therapeutic value and cost-effectiveness, the DGCCSF carries out a confidential reimbursement price negotiation with the sponsor. After reaching agreement with the sponsor, the DGCCSF sends its recommendations to the CIPM, which makes the final reimbursement decision [137].

It is unclear whether the above assessment process applies to all drugs. Before REvalMed NHS, TPRs were based solely on the clinical HTA conducted by AEMPS, with cost-effectiveness usually not being taken into consideration [138]. The criteria for pricing and reimbursement was based on the Royal Legislative Decree 1/2015 (RDL 1/2015) of the law on medicinal products indicating that the following factors are taken into consideration by CIPM: therapeutic and social value of the drug, incremental therapeutic value along with its cost-effectiveness, severity of disease and need for a specific group of patients, budget impact and innovativeness of the drug.

The role and methodology of economic evaluation is also unclear [139]. The sponsor is required to submit a detailed dossier, with incidence and prevalence information, the ex-factory price proposed by the sponsor, expected sales volume, the drug's price in other European countries, cost-effectiveness studies, and information on the impact of drug sales on the Spanish national and regional economy.

Two regional HTA agencies, the Galician Agency for Health Technology Assessment (AVALIA-T) and the Basque Office for Health Technology Assessment (OSTEBA), have developed guidelines to support disinvestment at the regional level. There is also a regulatory framework at the national level in the form of Royal Decree 1030, indicating that reassessment should be carried out if there is evidence of a lack of effectiveness or an unfavourable risk-benefit ratio, if better technology becomes available, or if the technology no longer meets regulatory requirements.

In 2010, OSTEBA developed a guideline for reassessment, the Guideline for Not Funding Technology (GuNFT), which suggested that disinvestment decisions should be informed by up-to-date and high-quality scientific evidence. A criterion for reassessment is that disinvestment must not lead to an absence of care or superior alternative treatment must be available. The guideline provides a detailed questionnaire to inform disinvestment decision. The outcomes of the process can be as follows. Disinvestment occurs as per the terms proposed, disinvestment is not approved but reassessment may occur in future, and disinvestment is not possible. It is not clear whether the disinvestment process is still in place [140, 141].

- **Flexibility, Predictability and Transparency**

No information was found regarding conditional approval, financial agreements or performance-based agreements at a national level. However, some regions do implement risk-sharing agreements (RSA), usually referred to as performance-linked reimbursement (PLR). One region, Catalonia, initiated RSAs in 2011 for hospital outpatient drugs. In these agreements, the Catalan Health Service, CatSalut, pays the reimbursement price upfront, but sponsors are required to pay a rebate for patients who did not achieve the anticipated benefits mentioned in the agreement [142].

In Spain, the outcome of the HTA process is not predictable, though submission guidelines are available to sponsors. There are no explicit thresholds for cost-effectiveness. The criteria or drivers influencing the reimbursement decision are not clear.

The TPR is shared with stakeholders, including sponsors, for their feedback. Sponsors are required to comment on the draft within 10 days. Comments are then incorporated into the revised TPR draft, which then informs price negotiation and reimbursement decision-making. The final version of the TPR is published on the AEMPS website after the pricing and reimbursement process has been completed, but confidential information is usually redacted [143].

- **Equity**

Spain has expressed commitment to ensuring “health, equity and sustainability” in prioritising technologies for assessment [136].

- **Stakeholder engagement**

Spain has engaged health professionals and industry in post-market evaluation [144]. It has also consulted health professionals in prioritising technologies for assessment [145].

Research suggests that, compared with “England, Sweden, France and Germany”, Spain “falls short” in relation to stakeholder engagement and other aspects of HTA [139]. However, Spain is reportedly progressing its stakeholder engagement, with the Spanish Network of Agencies for Assessing National Health System Technologies and Performance (RedETS) having developed a “Patient Involvement Strategy aimed to

promote patients' participation from the first phases" of HTA [146] (see also [147]). Methods have included "surveys, focus groups, in depth interviews, and participation in an expert panel", and the main challenges have related to recruitment and "capacity building" [148]. Spanish HTA researchers report that patient engagement:

> must be included in all HTA reports, except those that assess technologies with no relevant impact on patients' experiences, values, and preferences. Patient organisations or expert patients related to the topic of the HTA report must be identified and invited. These patients can participate in protocol development, outcomes' identification, [the] assessment process, and report review. When the technology assessed affects in a relevant way patient experiences, values, and preferences, patient-based evidence should be included through a systematic literature review or a primary study [149].

- **Special Pathways**

While there is no special pathway for high-cost treatments, increasingly treatments with a high budget impact and unclear long-term benefits are being reimbursed under specific arrangements, including RSAs, caps on the number of reimbursable units and rebates if established clinical benefits are not achieved. Due to Spain's decentralisation of market access and regions being responsible for allocating budgets for health services, there may be additional agreements with regional authorities for access to regional markets. In 2019, an online registry platform, "Valtermed", was created by the Ministry of Health to collect real-world data to reduce the uncertainty in the evidence-base of new therapies and to monitor benefits in clinical practice [150].

There is no special pathway for orphan drugs. However, a recent Supreme Court ruling stated that orphan drugs with no authorised therapeutic alternative can be excluded from a reference price system.

SWITZERLAND

Switzerland has a multi-payer health care system. Non-profit companies provide compulsory insurance, which covers 100% of the population [14]. Compulsory insurance provides the same coverage for everyone. The companies providing compulsory insurance should be recognised and supervised by the Federal Office of Public Health (FOPH). Compulsory health insurance is financed by individual premiums, co-payments, and federal and cantonal funding [151]. People can also have insurance for supplementary health care, where insurers operate for-profit [14]. Only the medicines on the Specialities list (SL/LS), which the FOPH draws up, can be reimbursed. The list sets the maximum price and tariffs for payment under mandatory basic health insurance. To be eligible for listing in SL, medicines should demonstrate Effectiveness, Appropriateness and Economic Efficiency (EAE) [152]. The EAE review is conducted reactively, and sponsors are required to submit the evidence dossier. The Health Insurance Benefits Division under FOPH evaluates whether medicines adhere to EAE principles [153]. The evaluation

has HTA components according to the background report for each listed medicine[154]. HTA assessment is conducted by the Health Insurance Benefits Division. The HTA report is appraised by Federal Commissions. FOPH decides whether mandatory reimbursement is terminated, restricted or continued[155].

A hybrid approach is used in Switzerland, where the HTA that occurs under the Health Insurance Benefits Division remit is reactive and the HTA that occurs under the Federal HTA programme is proactive. In the Federal HTA programme, anyone can propose topics. The Federal Medical Services Commission (ELGK) and the Federal Medicines Commission (EAK) will then make topic selections. External partners write the HTA protocol and report. The Federal HTA programme can also conduct HTAs that inform reimbursement when commissioned by the government, especially when the technology needs a full HTA (in-depth health economic clarification). The Federal HTA programme also informs disinvestment or the delisting of products that do not follow the EAE principles [155]. However, it is unknown to what extent the work under the Federal HTA programme directly informs medicine reimbursement.

- **Efficient HTA pathway**

No information is available on how long it takes for medicines to be listed on SL. An analysis showed that it took an average of 352 days for cancer medicines to be listed on SL since MA [156]. For the Federal HTA program, the deadline for topic identification is set on 1 March each year. After topic selection, it takes two months for pre-scoping, five months for the HTA protocol to be generated, and 6-12 months for the HTA report to be generated [157].

Medicines can be reimbursed in individual cases, even if Switzerland's regulator, Swissmedic, has not yet granted MA, but the product should have MA from a country with an equivalent health system [158]. To be reimbursed without MA, the medicine must represent an indispensable precondition for the provision of another essential treatment that SL already covers, its use must result in significant treatment benefit, or there must be no alternative in the market for the disease that is severe. Physicians are required to fill out a cost reimbursement form to the insurance provider before providing the treatment on an individual basis [158]. It is unclear whether HTA is required for this reimbursement approval.

Prioritisation occurs in the topic selection process under the Federal HTA programme, though the Swiss HTA programme does aim to delist and disinvest [155]. Prioritisation under the Health Insurance Benefits Division is unknown.

There is a regular reassessment process conducted by FOPH, which is called Triennial Review [159]. FOPH conducts a Triennial Review of all pharmaceuticals on SL every three years to evaluate whether they meet the three principles of listing. The requirements of Triennial Review and the medicines that will undergo it are published online yearly. The outcome of the Triennial Review directly impacts the price of medicines listed in SL.

- **Flexibility, predictability and transparency of HTA pathways**

The EAE review outcome is unconditional coverage, conditional coverage or no coverage. Therefore, the HTA outcome is flexible. However, there is no detailed document available on the EAE review. The reports explaining why medicines meet EAE are brief and in German [154]. Therefore, it is unknown whether the HTA process is flexible or predictable.

Under the Federal HTA programme project, the HTA report, scoping review and the stakeholder feedback are publicly available. However, information related to final HTA appraisal/decision making about funding is not available [160]. On the other hand, Health Insurance Benefits Division publishes summaries of its decision regarding the clinical and cost-effectiveness of medicines, however, no information is available on the evidence analyses [154]. It is also unclear whether sponsors can comment on the HTA report. Therefore, the transparency of the HTA process for sponsors is unknown; the transparency of all other stakeholders is partial due to the limited information in the report.

- **Stakeholder engagement**

Swiss HTA protocols are given to "health insurance associations, patient organisations, healthcare professional associations, professional societies, industry associations or other interested parties" for comment for 20 working days) [157]. The finalised protocol is published along with stakeholder comments [157]. Evaluation results are also made public [161].

SWEDEN

Sweden is characterised by a universal health system that covers the provision of health services to all legal residents. Administratively, there are three governance levels with the national government responsible for overall health policies whereas regional governments finance and deliver health care services to their respective regions and municipalities are responsible for providing services to elder and disabled populations. The funding for health services comes primarily from regional and municipal tax revenues. Furthermore, the national government also provides grants and subsidies to regions and municipalities through income and indirect taxes. The covered services included outpatient, inpatient, long-term care, prescription drugs, dental and mental health.

- **HTA Model**

The reimbursement and prices of pharmaceuticals and other medical devices are decided by a governmental agency under the Ministry of Health and Social Affairs, TLV. TLV assess the clinical and cost-effectiveness of a drug based on the detailed dossier submitted by the sponsor. Additionally, the government may also commission Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) to

conduct HTA assessment to inform the reimbursement decisions and price negotiations for medicines. Along with the commissioned HTA assessment reports, the SBU also conducts HTA proactively. The topics for HTA assessment may be suggested by various sources such as government, decision-makers, and other relevant Swedish agencies as well as SBU Scientific Advisory Committee [162]. The HTA recommendations provided by either TLV experts or SBU are appraised by a separate expert board within the TLV; the Pharmaceutical Benefits Board. This board comprises seven experts representing regions, clinical and health economic expert centres and patient groups. These members are appointed by the government. The assessments are based on three criteria: clinical value; need and equity considerations and cost-effectiveness.

Sweden is also a part of the Nordic FINOSE collaboration which allows agencies from Sweden, Finland and Norway to cooperate on the HTA assessment and write joint assessment reports.

- **Flexibility, Predictability and Transparency**

The HTA appraisal is flexible as there are risk-sharing agreements in place to reimburse drugs that otherwise would not be reimbursed due to uncertainty in the evidence base or high budget impact. From 2014 till 2022, drugs from seven therapeutic classes were reimbursed under risk-sharing agreements such as MEAs to address uncertainty in the evidence base or limit the budget impact or maximise the effective use. Such agreements, however, do not affect the listed price but can impact the cost of treatment for different regions.

The severity of the condition is one of the main factors in determining which treatments will be reimbursed by the TLV. Therefore, varying thresholds of cost-effectiveness were considered acceptable in different assessments depending upon the degree of severity of the indication. For instance, in the last few years a threshold of 1,000,000 Swedish kronor (SEK) per QALY was considered acceptable for highly severe conditions, whereas 750,000 SEK/QALY was accepted for severe conditions and 500,000 SEK for moderately severe conditions. However, academic literature indicates that there are different approaches to assessing the severity of a condition leading to inconsistencies in the decision threshold [163].

There are guidelines available on the TLV and SBU websites outlining the requirements of the applications for the sponsors. The HTA methods used to assess the application are also provided on the website. However, the information is not in the English, therefore, it is difficult to determine whether the available information is adequate to make the evaluation process predictable for the sponsors.

The assessment reports are published in the Swedish language on the TLV website, however commercial and academic confidential information is redacted.

- **Equity**

Sweden's methods guidance highlights impacts on “equity, justice, autonomy, integrity and structural factors with ethical implications” [164].

- **Stakeholder engagement**

In Sweden, producers of HTA reports collaborate with experts and patients, and reports are reviewed by independent experts [165]. The prioritisation of research projects is based on the perspectives of patients, their relatives and healthcare staff concerning which research gaps are most urgent to close [165]. "In Sweden, a new reimbursement application may lead to the establishment of a patient reference group consisting of two patient representatives from relevant patient organisations" [88].

- **Special Pathways**

Though there is no specific pathway for the assessment of high-cost treatments or ATMPs in Sweden, however, TLV adopts value-based pricing models in assessment. This can favour advanced treatment or treatment for high unmet clinical needs. There is also flexibility in the ICER threshold (as discussed above) based on the three principles of the assessment process: equity (human value), need and cost-effectiveness. The willingness to pay can vary on a case-to-case basis based on equity and need for the drug.

TLV is also working on developing payment models for high -cost treatments that can balance innovation with cost control [166]. Similarly, medicines for populations with high unmet clinical needs are assessed through the same pathway as other medicines, however, funding decisions are influenced by medical need, therefore, there may be a higher willingness to pay or flexibility in the ICER threshold for medicines for conditions that are rare and/or have a high unmet clinical need.

In Sweden, drug submissions with uncertainties relating to clinical and cost-effectiveness can be conditionally reimbursed through non-outcome-based managed access and/or coverage with evidence development agreements subjected to reassessment. The academic literature indicated most of these agreements aimed to reduce cost-effectiveness uncertainty. Such agreements are usually negotiated under the protocol proposed by the NT council for the managed introduction of new pharmaceuticals. However, for outpatient drugs, there is no framework for such agreements and mostly decided on the generic reimbursement conditions, but decisions are usually taken on a case-by-case basis depending upon the clinical need [167].

Similarly, there is no special pathway for the assessment of codependent technologies, however, the Government of Sweden has recently mandated the TLV to develop methods for health economic evaluations of precision medicine and ATMPs. In a report ", TLV addressed how uncertainties in cost-effectiveness can be quantified and managed. The report stated that the evaluation of precision medicine is no different from the evaluation of other treatments with the uncertain evidence base [168]. However, it is not clear whether the recommendations provided in this report are incorporated into the assessment of precision medicine.

In 2018, the Swedish government commissioned the Public Health Agency of Sweden (PHAS) to pilot a supply-based reimbursement process for antibiotics with significant

medical value and ensure patient access to antibiotics required to treat drug-resistant infections. The antibiotics selected for this pilot program should have special medical value, risk of lack of availability on the Swedish market and annual sales must not have exceeded SEK 4 million during the previous year 2019. In this supply-based reimbursement model, the national government guarantees a minimum annual revenue to the manufacturers of selected antibiotics and in return, the company is required to ensure the supply and stockpile of selected antibiotics within an agreed time frame. In this model, the reimbursement of antibiotics was partially de-linked from the sales revenue. The results of this pilot program were presented to the Swedish government in March 2023 and the official implementation of this model is under consideration [169].

TAIWAN

The Centre for medicine evaluation (CDE) is a centralised national HTA agency that carries out assessment of health technologies. The HTA process in Taiwan is reactive; sponsors are required to submit an application to the national health insurance administration (NHIA) for funding. The CDE conducts assessment of the evidence submitted by the sponsor for clinical and costs effectiveness. The assessment reports are appraised in the Expert Advisory Meeting (EAM), and the recommendations are provided to the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) joint committee for final decision on funding the medicine [170, 171].

- **Efficient HTA pathways**

From the submission of evidence by the sponsor to reimbursement decision takes an average of 436 days [171]. There is a disinvestment process for all listed medicines. From 2010, new medicine applications are classified into three categories for pricing purposes based on the clinical evidence[171]:

- Category 1: for direct comparison with the appropriate comparator or indirect comparison with clinical studies. The clinical studies indicate significant improvement in the clinical efficacy.
- Category 2A: for direct comparison with the appropriate comparator and clinical evidence suggests moderate improvement in clinical efficacy.
- Category 2B: for medicine with similar or equivalent clinical value to the referenced drug.

The reimbursement levels are determined by PBRS joint committee based on the HTA assessments. The reimbursement price can change based on the periodic market survey by NHIA [172].

- **Flexibility, predictability, and transparency of HTA pathways**

The HTA guidelines used by CDE are available online, however, these are not in English, therefore, it was not possible to determine the flexibility and predictability of the HTA process [173]. According to the law, the PBRS joint committee meeting agendas, HTA

reports, and meeting minutes need to be made public and delivered to meeting representatives seven days before the meeting [174]. Sponsors can comment on the HTA report within seven days[175].

- **HTA pathways for specific technologies and populations**

Orphan medicines can listed on the NHI Pharmaceutical Benefits and Reimbursement Scheme before marketing authorisation is granted. However, sponsors for such medicines should apply for MA within three years after being listed. Otherwise, it will be delisted [176, 177].

The literature indicates that innovative therapies such as gene therapies with uncertain long-term clinical outcomes have been conditionally funded in Taiwan through risk-sharing agreements [177]. The agreements may include price-volume, outcome-based and financial agreements[177].

- **Equity**

Taiwan's methods guidance for cost-benefit analysis features extensive text on equity, showing particular regard for "the elderly, low income households, people in remote areas", "equal opportunities to receive medical care, regardless of age or gender", socioeconomic status, or comorbidity [178] (see also Taiwan's guidelines of methodological standards for pharmacoeconomic evaluations [179]. The guidance discusses whether QALYs should be weighted more at the end of life. In Taiwan, there is a formal requirement of the economic model to state any assumptions (implicit or explicit) about equity, including affected sub-groups defined by equity factors like the above [178] (see also Taiwan's guidelines of methodological standards for pharmacoeconomic evaluations [179]. Methods guidance for drug evaluation shows regard for distributional considerations ("who gains, who loses") [179].

- **Stakeholder engagement**

Taiwan makes use of clinical expert opinion for supplementary data. Taiwan shares a lot of detail on its patient involvement, which includes online meetings [180]. Online meetings were implemented in response to COVID-19 and a government-built online platform also "allows patients to submit their opinions" [180] (see also [181]). The final HTA reports are "discussed with patient representatives" then made public online [180]. In 2015-2020, "30 patients' insights were published" (19 relating to oncology) before the Joint Committee meetings [180]. Challenges remain around "timely patient engagement … provision of relevant resources", and improving "the visibility of patient input" [180]. The Pharmaceutical Benefit and Reimbursement Scheme (PBRS) has had two patient representatives since 2019 [181]. Disease-specific patient representatives will also be invited for resubmissions [181]. The Center for Drug Evaluation (CDE) has helped with patient engagement since 2020 [181]

THE NETHERLANDS

- **HTA Model**

For admission of a medicine to the standard health care benefits package (GVS, the Medicine Reimbursement System), sponsors are required to submit an application to the Ministry of Health, Welfare and Sport (VWS). This is done after receiving market authorisation from the European Medicines Agency (EMA) or Medicines Evaluation Board (MEB). The national HTA body, the Dutch National Health Care Institute (Zorginstituut Nederland; ZIN) assesses medicines and technologies for inclusion in the GVS based on four criteria: effectiveness, cost-effectiveness, necessity, and feasibility. In preparing its advice, ZIN takes into consideration the opinion of a Scientific Advisory Board (WAR) comprising 50 external, independent experts. Other stakeholders, such as health insurers, physicians and patient groups, are also consulted at this stage. The HTA report is revised based on the feedback received from the WAR and in most cases reassessed by WAR before recommendations are made. The recommendations provided by ZIN are also appraised by the Insured Package Advisory Committee (Commissie Pakket; ACP).

ACP comprises independent experts appointed by the Ministry of Health, Welfare and Sport (VWS). Their expertise ranges from clinical practice and patient representation to ethics and health economics. If a major impact on the health care budget or a major social effect is expected, ACP appraises the procedural and policy issues that relate to weighing effects from a societal perspective, such as the availability of alternative drugs, equity, and orphan status of disease. In the final phase, the executive board of ZIN formulates their recommendations to the VWS regarding the inclusion of the technology in the health care benefits package based on the information obtained in the assessment and appraisal phases [182].

Since 2016, VWS and sponsors have negotiated on a per-product basis multi-year-multi-indication (MYMI) agreements for oncology drugs with multiple indications. These provide a comprehensive framework for multiple indications, rather than assessing an individual drug for each indication separately. Each sponsor has a separate but confidential agreement, under which the drug may not need to go through a full HTA assessment by ZIN if it receives approval from an oncology appraisal committee (Commissie Beoordeling Nieuwe Oncologische Middelen; CieBOM). However, reassessment may be possible in case of clinical uncertainty for all drugs approved under the MYMI agreements [183].

Disinvestment may occur indirectly through withdrawal by the sponsor or in the case of conditional reimbursement or CED, where pharmaceuticals are reassessed after a predetermined time. In most cases this is 4 years, when additional evidence, if available, can result in a disinvestment decision [184].

- **Flexibility, Predictability and Transparency**

The Dutch HTA process is flexible, with no fixed timeline or cycle from submission to VWS consideration. The outcome of the HTA process is not limited to recommendation or rejection; some drugs are given conditional financing, specifically under coverage with evidence development (CED) agreements. A drug needs to meet three criteria to qualify for conditional financing: there must be (1) a budget impact higher than €2.5 million per year, (2) uncertainties regarding cost-effectiveness in clinical practice, and (3) proven added clinical value. After receiving conditional financing, the market authorisation holder needs to conduct an outcome research study (usually over three years), whose results are submitted to the HTA agency for reassessment. According to ZIN guidelines, a drug nominated for conditional financing would go through a standard assessment process, but ZIN would reassess the drug after four years for therapeutic value, appropriate use, cost-effectiveness and budget impact [185].

ZIN uses a deliberative process to determine whether additional criteria should affect its initial recommendation and to reach a final recommendation. The Scientific Advisory Board (WAR) and the Insured Package Advisory Committee (ACP) advise the National Health Care Institute in the HTA assessment. The assessment outcome is influenced by the quality of the evidence, patient perspectives, budgetary constraints, and societal values. Therefore, it is not possible for sponsors to predict with certainty the outcomes of an HTA evaluation or what pharmaceutical price would result in a recommendation.

The decision made by VWS is transparent. The final outcome of a decision-making process is published in the Law Gazette (Staatscourant).

- **Equity**

Dutch academics have advised on using “equity weights” and concepts of need such as “proportional shortfall” in HTA [186]. “Fair distribution” is acknowledged as a goal, with reference being made to “normal health state at different ages” [186] and “investment that is worthwhile” in connection to conditional reimbursement of specific technologies [187].

- **Stakeholder engagement**

In the Netherlands, diverse stakeholders (including clinicians, HTA experts and ethical and legal experts) have been engaged to inform the implementation of specific technologies, such as whole-genome sequencing [188] and orphan drugs [189]. Dutch academics have conducted many research projects into HTA methodology [186]. “Public and patient participation” has been mentioned but limited in relation to HTA methodology research [186].

- **Special Pathways**

There is no special pathway for first-in-class or first-in-indication medicines, however in 2015 a new set of rules were introduced for high-budget-impact medicines, including those first-in-class and first-in-indication. Any product expected to cost over €50,000 per patient per year with a budget impact of €10m, or with an overall budget impact of €40m or more per year, is placed under a ‘lock system’. This suggests that these

products are excluded from the basic insurance package until financial and price negotiations are informed by HTA assessment. Products are removed from the lock system only after agreement has been reached between the sponsor and VWS, enabling reimbursement for eligible patients at a socially acceptable price. For example, the first immuno-oncology products to market, such as Keytruda and Opdivo, were placed on a lock system until a negotiated agreement was reached [190].

There are no special pathways for co-dependent technologies or personalised medicines, but at the request of VWS, ZIN published its advice on optimal use, reimbursement and funding pathways for co-dependent technologies and personalised medicines in December 2020 [191].

Historically orphan drugs were not assessed and automatically qualified for reimbursement upon registration as hospital drugs. An orphan drug is made available to patients at a price set by the manufacturer, as long as the drug's annual budget does not exceed €2.5m. However, the 'lock' system was piloted in 2015 and formalised into law in 2018 by the VWS in response to fiscal pressure on hospital budgets. As a result, orphan drugs that enter the lock system based on the criteria mentioned above now undergo HTA prior to a reimbursement decision and during this time the drug is not included in the health care benefit package.

UNITED KINGDOM

England

All English residents are entitled to free public health care under the National Health Service (NHS). The NHS is funded by the national government through general taxation. The NHS England, which is a government agency, allocates funds to different Clinical Commissioning Groups, which pay and govern healthcare delivery at the local level. Moreover, 10.5% of the population also have voluntary supplementary insurance for access to elective care.

- **HTA Model**

In England, an independent HTA body, the National Institute for Health and Care Excellence (NICE), is responsible for conducting the assessment of new health technologies for clinical and cost-effectiveness. First, NICE produces a list of provisional appraisal topics for technology appraisal guidance so that the topic selected will add value to the quality of care and provide best value for money. Many academic and non-academic institutions are involved in informing NICE regarding new and emerging technologies and topic selection, such as the National Institute for Health Research Innovation Observatory at the University of Newcastle and relevant companies on the NHS Innovation Service and_UK PharmaScan. Researchers, patients and healthcare professionals can also suggest topics for appraisal by contacting the National Institute for Health Research Innovation Observatory. The topic selection process can take 4-12 weeks [192]. NICE then identifies the consultees, such as bodies representing different

stakeholders, the Department of Health, the Welsh government, NHS England, the company that holds the market authorisation for the technology selected for the appraisal, and clinical commissioning groups. The consultees can make a submission for the HTA as well as provide consultation on the appraisal consultation document. NICE is responsible for developing the scope of the appraisal process but can only begin to appraise a technology when it is referred to do so by the Secretary of State for Health. After the appraisal topic referral, the company is invited to submit a comprehensive and concise report on all the available evidence for single technology appraisal (STA). For multiple technology appraisal, NICE can invite multiple consultees to provide a submission. NICE commissions independent academic groups called evidence review groups (EAGs) to prepare an assessment report, which is then appraised by an independent advisory committee and provides provisional recommendations in the form of a Final Appraisal Document (FAD). Different consultees and commentators are given four weeks to comment on the final document. However, if the appraisal committee does not recommend the use of the technology, limits the use beyond what was specified in the market authorisation, or seeks further clarification from the company on the key evidence submitted, then an Appraisal Consultation Document (ACD) is produced, which is open to public consultation for four weeks. After the closing of public consultation, the appraisal committee again considers comments and finalises its recommendation in the form of an FAD for inclusion of the technology in the NHS. The final recommendations are issued as NICE guidance [193].

There are no fixed timelines for different stages of the appraisal process. The timeline can vary depending on the nature and process involved in the appraisal. For technologies where no ACD is produced, the HTA outcome comes approximately 26 weeks after NICE invites organisations to participate in the appraisal as consultees or commentators. The expected timeline for the appraisal process if an ACD is produced is 30 weeks. The Evidence Review Group (ERG) has approximately seven weeks to provide an evidence report to NICE. The sponsors are provided four weeks to provide comments on the evidence report. When funding by the NHS is recommended, regulations require that patients have access to the technology within three months, except when there are specific barriers to implementation within this period [192].

NICE implements prioritisation in the HTA assessment process through topic selection. The purpose is to choose an innovative and emerging topic for HTA that will add value and support healthcare professionals in providing the best quality care and offer best value for money. In 2022, a new proportionate approach was also introduced in case not all technologies need to go through the full appraisal process. This approach allowed faster and less rigorous evaluation for low-risk treatment. NICE will not provide guidance on any technology that has not received market authorisation in the UK.

- **Flexibility, Predictability, Transparency**

The HTA outcome is flexible, with the committee providing varying recommendations based on the potential benefit to the patient and health and social care system shown

in the evidence. The type of recommendations provided are: positive recommendation, recommended in specific circumstances (or population), recommended with managed access, recommended with data collection (uncertainties in evidence can be addressed), only in research, and not recommended [192]. To increase access to new innovative drugs, some drugs may also be approved with managed access agreements between a company and NHS England due to uncertainty relating to cost and clinical effectiveness. This is a time-limited agreement (maximum five years) under which patients can access NHS-funded treatment while data is collected to address uncertainties.

The HTA process is partially predictable, since a detailed manual and the methods used for HTA appraisal are available on the NICE website. However, HTA appraisal also encompasses the assessment and consultations with patient, clinical and commissioning experts, incorporating different health, social and economic considerations. Therefore, it is not possible to predict the outcome of a HTA appraisal with certainty. In terms of cost-effectiveness, NICE uses an explicit cost-effectiveness threshold of £20,000 to £30,000 per QALY gained for its decision making. Generally, drugs with an ICER below the lower bound are considered cost-effective, whereas drugs with an ICER above the upper bound are not considered cost-effective. For submissions with ICERs above £20,000/QALY, additional factors (such as the nature and extent of innovation in the technology, and uncertainty surrounding the ICER and health utility not fully represented in the ICER estimation) are considered important for decision making. Drugs meeting the end-of-life criteria can be recommended with an ICER higher than the conventional ICER range. This reflects the importance of social value judgements in the NICE deliberation process, with end-of-life treatment being given more weight than other treatment [194].

The final appraisal document is published on the NICE website. However, confidential information is removed. NICE also publishes a lay version of its recommendation, known as 'Information for the Public'. In many cases, NICE accepts unpublished data as evidence under a confidentiality agreement. Such evidence can be academic-in-confidence (public disclosure would limit the ability to publish the evidence in scientific literature) and commercial-in-confidence (public disclosure impacts the commercial interests of a company). The academic-in-confidence evidence can be presented at an appraisal committee meeting attended by members of the public [192]. Company or sponsor representatives participate at the committee meeting, but will not have access to any confidential information or appendixes created by an external assessment group for an evaluation of a comparator that is under a confidential commercial arrangement.

- ***Equity***

NICE welcomes the submission of evidence concerning patient subgroups "who may need special consideration" [192]. NICE specifies that "in specific circumstances" QALYs may be weighted in view of equity considerations [192]. Specifically, the severity of the medical condition may be considered in terms of "absolute and proportional QALY shortfall" (how much health people stand to miss out on) [192]. For "highly specialised

technologies", the size of the benefit may be considered [192]. NICE established the Highly Specialised Technologies Programme specifically to achieve "more equitable treatment access for very small populations with very rare diseases" [192]. One author claims that a different ICER threshold is used for highly specialised technologies [195]. NICE states that patient subgroups may be defined by geographical location, for example when costs differ with geography. NICE recognises that health inequalities may be related to geography [196]. NICE recognises that its decisions can bear "on broader social considerations" and articulates "social value judgements" to which it is committed and which were formed through public engagement [192]. NICE relies on the ICER and recognises that this involves rejecting the 'rule of rescue', referred to as "the desire to help an identifiable person whose life is in danger no matter how much it costs" [192]. NICE expressly aims to "reduce and not increase identified health inequalities" and to "improve population health as a whole" with due regard to the people "most disadvantaged" [192]. NICE thinks about equality in terms of "the protected characteristics stated in the Equality Act 2010 [192], which are age; disability; gender reassignment; marriage and civil partnership; pregnancy and maternity; race; religion or belief; sex; and sexual orientation [192]. NICE also takes into account "inequalities arising from socioeconomic factors and the circumstances of certain groups of people, such as looked-after children and people who are homeless [192].

NICE has recently garnered critique for moving away from its 'Social Value Judgements' document to a 'Principles' document which, the critique proposes, focusses more on its equity-related procedures than substantive moral considerations [195]. 'Social Value Judgements' provided substantive guidance on some over-arching moral considerations and was produced through an exercise in deliberative democracy involving some 50 demographically representative members of the public (the Citizens Council). Principles, by contrast, "tells NICE's stakeholders much about how the organisation goes about the process of decision-making, [but] it tells them little about the substantive grounds on which its decisions are now based" [195]. Therefore, "given NICE's reliance on transparency as a requirement of procedural justice, NICE does not in this respect satisfy its own specification of a just decision-maker" [195].

- **Stakeholder engagement**

NICE draws on clinician and academic expertise to offers advice to industry on science and engaging patients [197]. NICE welcomes the submission of evidence concerning the experiences and views of patients, carers and treating clinicians [192]. Evidence is reviewed by an independent academic group and numerous stakeholder groups [192]. NICE has a Public Involvement Programme to promote the involvement of service users, families, carers, and the public "regardless of disability, language, or other potential barriers"[198], where a "public involvement adviser is assigned to each evaluation" [192]. Consultations are open to community organisations, health and social care professionals, industry, and local government, who are invited to comment on potential

"health inequalities" [198]. NICE's Highly Specialised Technologies Programme gives extensive regard to consultation, including public consultation.

With COVID-19, NICE shifted to online patient engagement, which patients "felt to be more accessible and inclusive" but it restricted opportunities "to form interpersonal relationships between committee members", "to bounce ideas off each other", and to gauge people's reactions [199].

A detailed flowchart of patient involvement at every stage, from the scoping phase through to the final decision and possible appeal, is available [200].

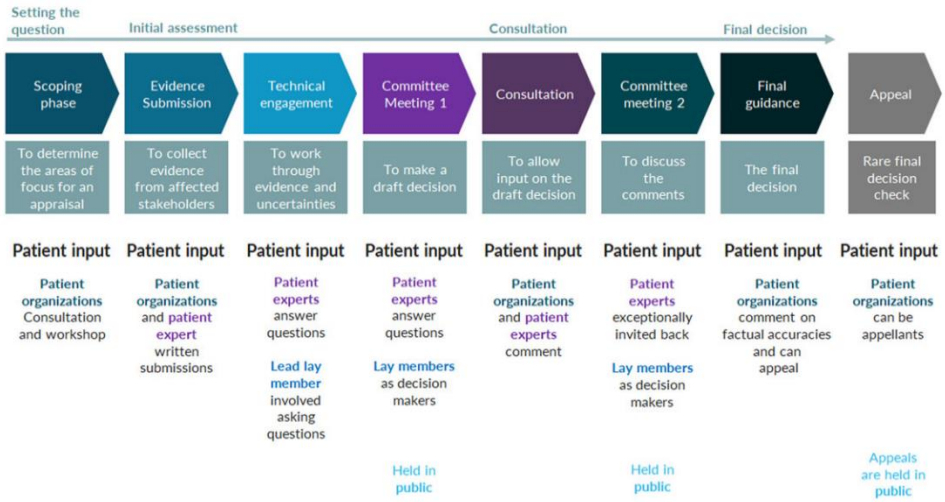

Figure 1. Stages of patient involvement at NICE. Diagram showing the types of patient involvement at the different stages of a typical medicines HTA. HTA, health technology assessments; NICE, National Institute for Health and Care Excellence.

The below table summarises stakeholder engagement in the UK and is copied from. [7].

Stakeholder Engagement*	**HTA Committee Representation**	**Patient Involvement**	**Appeals**	**Transparency**
Consultees can submit evidence during the appraisal, comment on the appraisal documents, and nominate patient experts and clinical specialists Commentators are invited by NICE to take part in the appraisal process and comment on the various documents	Manufacturers NHS (payers) Physicians Patients (as lay members) Academics Lay backgrounds Committee members are appointed for a three-year term, and are drawn from NHS, patient and carer organisations, academia,	-The Public Involvement Programme (PIP) at NICE supports and develops public involvement - A PIP adviser is assigned to each appraisal and supports patient and carer organisations, their representatives, and individual patients or carers	-All consultees have the opportunity to appeal recommendations, or report any factual errors, in the final appraisal document -Commentators cannot appeal the final appraisal determination -More about grounds for appeal	- Evidence on which the appraisal committee's decisions are based is made available to stakeholders and is publicly available - In some cases, unpublished evidence is accepted under agreement of confidentiality - Appraisal committee

produced during the process	pharmaceutical and medical devices industries	throughout the appraisal	meetings are usually open to members of the public and press

Wales

In Wales, the HTA appraisal of new drugs is performed by the All-Wales Medicines Strategy Group (AWMSG) or by the National Institute for Health and Care Excellence (NICE). NICE recommendations are applicable in both England and Wales. Therefore NHS Wales will be able to access a drug if recommended by a NICE HTA process. In cases where NICE conducts a HTA appraisal of a drug that has already been appraised by AWMSG, NICE guidance can replace AWMSG's advice. AWMSG uses the NICE guidelines and criteria to assess clinical and cost-effectiveness. The topic selection for HTA appraisal by AWMSG also depends on the future work programme of NICE, as AWMSG usually does not perform HTAs of drugs for which NICE published guidance within 12 months of market authorisation. Wales also has a national HTA body, Health Technology Wales (HTW), but it carries out appraisals of medical devices, diagnostics, procedures, and interventions by allied health professionals only. It does not perform appraisals of medicines.

Health boards in Wales are required to make medicines available to patients within two months (60 days) of the publication of NICE guidance.

- **Equity**

There are implied equity concerns when mentioning patient groups who might be able to benefit more or less than others, with specific mention of patients "who are unable to have surgery, or those who have other diseases, those in rural areas who cannot access services" [201]. Health Technology Wales is expressly interested in equity in terms of the potential of a health technology "to introduce, increase, or decrease equity" [202].

- **Stakeholder engagement**

The All Wales Medicines Strategy Group contains "healthcare professionals, academics, health economists, pharmaceutical industry representatives and lay representatives" [203]". It engages "patient interest groups" [203]. Since its establishment in 2002, it has met in public, namely with members of the public able to attend and view deliberations. Health Technology Wales contains "Researchers, Health Economists, Information Specialists, and Patient and Public Involvement (PPI) professionals" [202].

Scotland

All the residents in Scotland are also entitled to free public health care under the National Health Service (NHS). The NHS Scotland operates as 14 territorial health boards

who have responsibility for the health of their populations and funded by the national government through general taxation. An independent HTA agency, Scottish Medicine Consortium (SMC) provide the recommendations to NHS Scotland on the clinical and cost-effectiveness of newly authorised drugs from the Medicines and Healthcare products Regulatory Agency (MHRA) or the European Medicines Agency (EMA), new formulations and new indications for medicines which have already been assessed by SMC.

- **HTA Model**

SMC carries out HTA appraisal as a response to a submission by company/sponsor holding market authorisation. The New drug committee (NDC) reviews the evidence and produces an assessment report. For general medicines, if NDC give positive opinions to the medicines, the advice would be issued to the health boards following SMC executive review. A negative opinion can be also issued but sponsors are able to provide new or improved patient access scheme before the medicines were discussed in the SMC meeting. For end-of-life care or orphan medicines, which are usually not cost-effective, opinions from patients and clinicians are more weighted, where Patient and Clinicians Engagement (PACE) meeting hold and the summary of the meeting will be included in the submissions[204].The patient group submission(s), clinical expert comments, NDC report and summary of the PACE meeting (if applicable) is finally submitted to SMC committee who will vote on whether to include a drug for NHS use in Scotland or not based on the evidence submitted. Especially, SMC introduced a new pathway in 2020 that allows abbreviate submission for me-too medicines, which provide faster access of medicines, reduce the time and demand of workforce, and helps SMC to make streamline decision[205]. Sponsors were required to filled Abbreviated Submission Form to the SMC Secretariate. The abbreviated submission advice for abbreviated submissions will be issued following SMC executive review rather than full committee consideration[206].

(SMC) committee comprises of a care team including health economists, pharmacists, public involvement professionals and administrative staff, representatives of NHS board, clinicians, and representatives of pharmaceutical industry and public. The SMC meetings are open to the public, and they can participate in the discussion by registering for a SMC meeting. The SMC decision will be made public approximately within 4 weeks.

In February 2012, the Scottish government issued guidance under the SGHD/CMO(2011)3 stating that NHS Scotland board is expected to reach a decision regarding access to drugs which have been recommended by SMC within 90 days of the issue of SMC recommendations to the NHS board and then publish this decision on website within 14 days of reaching that decision [207]. The SMC allows prioritisation in the submission but only in resubmission. In 2020, SMC introduced fast-track resubmission where the only change in the submission is an improved or new patient

access scheme (PAS) [208]. However, an extra one to three months are needed in the timeline if the PACE meeting conducted.

In Scotland, the market authorisation and HTA process is partially aligned especially for drugs that address a high unmet clinical need for life-threatening and highly debilitating conditions. This include medicine with conditional regulatory approval, Early Access to Medicine Scheme, and Innovative Licensing and Access Pathway, which full market approvals are not yet granted. SMC allows interim acceptance for drugs, but the future access depends on ongoing re-assessments. A full submission is needed if medicines convert MA status from conditional to full. The disinvestment in Scotland falls in the remit of heath boards. National Procurement works on behalf of the boards at a national level to leverage value from loss of market exclusivity.

Flexibility, Predictability and Transparency

SMC HTA final outcomes are flexible as the outcome is not limited to accept and reject, but also recommends some drugs with certain restrictions. These restrictions are related to recommendation of the drug in a particular patient group and typically based on company/sponsor request in their submission. Some drugs are also accepted on an interim basis if the committee considers that the drug provide value for money, but further evidence is required to address the uncertainties in the evidence. In such cases, drug is accepted for use subjected to further reassessment when further evidence is [209] available. The HTA process is also partially flexible with no set cycles, but timelines are roughly defined which can extend by 1- 3 months for a specific class of drugs (I.e., end-of-life and orphan drugs). Approximately, HTA process comprise of 8 weeks for assessment and provisional recommendations by the New Drugs Committee, 6 weeks for the appraisal and subsequent advice by the SMC and then 4 weeks for making that advice public.

The timing of the appraisal process is predictable, and methods and approach used for appraisal is publicly available on the SMC website. However, it is not possible for companies to predict with certainty the outcome of HTA process due to the complexity of the appraisal process involving evidence submitted by company, patient groups and wide-ranging stakeholders. The extent to which certain characteristics of the evidence and threshold at which decision would change from recommend to reject is not clear. Moreover, SMC may also accept a drug with a cost per QALY £20,000 and £30,000 if the provided evidence can prove significant benefit over the existing treatment/comparator [210]. In some cases, drugs with a cost per QALY above £30,000 may also be accepted if additional factors called ‘modifiers’, such as improvement in quality of life (with or without survival benefit), benefit for a sub-population of patients and bridging to another definitive therapy for some patients, can indicate added benefit [208]. The SMC committee meetings can be attended by wide range of stakeholders including pharmaceutical company representatives, patient group representatives and members of the public. However, these meetings can be conducted in private sessions when committee needs to discuss an information which is regarded as commercial in

confidence. The final outcomes are published on SMC website with confidential information redacted [210].

- **Equity**

The Scottish Medicines Consortium implies regard for some version of equity when it states that it considers "all patients who need treatment, not just those who may be treated with the medicine under consideration" [211]. It allows the use of "equity weights for QALYs" when industry, clinicians or patients highlight that a sub-group of patients may "derive specific or extra benefit", such as in the absence of "other therapeutic options of proven benefit".

- **Stakeholder engagement**

The Scottish Medicines Consortium holds its meetings in public. In 2015 it established a Public Involvement Network Advisory Group to engage "patients, carers and members of the public" [210]. There is also a dedicated Patient and Clinician Engagement (PACE) process [210] that can be used "for medicines used at the end of life and for rare conditions (orphan medicines)" [212]. A patient and public reference group was also established for specific technologies, namely the innovative licensing and access pathway [213]. Health Improvement Scotland gives industry opportunity "to comment on the factual accuracy of what is said about their product" by competitors in their submissions [214].

UNITED STATES OF AMERICA (USA)

- **HTA Model (for ICER only)**

An institute independently involved in the HTA activities is the Institute for Clinical and Economic Review (ICER). It is an independent not-for-profit organisation that assesses the clinical and cost-effectiveness of prescription drugs, medical tests, and other health technologies. The ICER evidence reports provide price benchmarks for different technologies based on clinical and cost-effectiveness, which can be used by individual payers in their price negotiations and coverage decision-making. Its recommendations are largely used to inform coverage decisions by Medicaid agencies, commercial insurance companies, and pharmacy benefit managers (PBM). ICER conducts HTA proactively, where the process begins with topic selection. The topic is selected based on a list of key criteria such as projected timing of FDA approval within one year, project budget impact, stakeholders' priorities, significance to the public and topics involving vulnerable populations[215]. ICER conducts horizon scanning of new and emerging technologies and stakeholders can also submit suggestions for a topic for an HTA.

The ICER assessment process comprises three main phases: topic selection and scoping, evidence assessment (clinical and cost-effectiveness and budget impact) and appraisal (public meeting of one of ICER's core programs). In all three phases, stakeholders are involved, and the final reports incorporate stakeholder's input. The scoping document

is published on the ICER website approximately 10 weeks after the topic selection whereas the timeline of the full HTA report is not reported[215]. However, after topic selection, the ICER began its assessment process approximately eight months before the expected decision on the market authorisation approval from the U.S. Food and Drug Administration (FDA). The purpose is to ensure that the final report and public hearing align with upcoming FDA decisions when paying bodies such as insurance companies or CMS make initial coverage decisions and negotiate prices[215].

- **Flexibility, Predictability and Transparency**

The HTA appraisal is partially flexible with CMS providing conditional coverage approval in certain cases where there is limited evidence. In recent years many technologies have come to market in earlier phases of the technology development lifecycle. This has resulted in limited or developing evidence for the clinical or cost-effectiveness of the technology. When available evidence is insufficient to show that technology is reasonable for diagnosis or treatment of an indication, coverage with evidence development (CED) has been used by CMS to support evidence development while ensuring early access to patients. The CED guidance document indicates that health technologies under Part A and Part B of Medicare coverage that fall within the statutory benefit category are considered for CED, which indicates that CED may be limited to drugs administrated at a physician's office or in a hospital outpatient setting [216]. Due to the requirements of MDRP, Medicaid programs do not have the same authority to limit or restrict drug coverage on the basis of the available evidence.

The general method and process guidelines are available on ICER websites which are regularly updated. Moreover, a scoping document is also published for each assessment before the evidence report. The scoping document not only outlines the detailed PICO (population, Intervention, Comparator and Outcome) but also outline the time horizon over which outcomes will be assessed, the study design of studies included in the assessment, the source of evidence and the proposed modelling framework.

ICER uses a common set of cost-effectiveness thresholds for all assessments including those for high-cost treatment and ultra-rare diseases. Along with QALY, ICER also includes the calculation of the Equal Value of Life Years Gained (evLYG) in its assessment to represent the gain in life years irrespective of improvement in the quality of life. The purpose is to reduce the risk of discrimination against any specific patient group. The health-benefit price benchmark used in ICER reports is $100,000-$150,000 per QALY and evLYG.

All reports are published on the ICER website, including research protocol (scoping document), model analysis, evidence report, stakeholders' input, ICER response to stakeholder's comments, and public meeting summary. Moreover, all ICER meetings are public and are live streamed and all stakeholders including members of the public can participate in these meetings [215, 217].

- **Equity**

The US Agency for Healthcare Research and Quality (AHRQ) recognises that "obtaining appropriate data for modelling from a societal perspective can be challenging (e.g., accommodating equity concerns)" [218]. Meanwhile, the Institute for Clinical and Economic Review (ICER) includes "Society's goal of reducing health inequities" (caused by historical determinants) as a specific category of "potential other benefits or disadvantages" for deliberation and voting on "by the independent appraisal committee at each public meeting" (noting a minor of major effect on the value of the technology) [217]. ICER opts for this approach because it does "not believe there are reliable methods to [quantitatively] weight QALYs gained by patients from disadvantaged" groups[217]. In view of a lack of academic consensus, ICER thinks it "premature to seek to create a separate series of cost-effectiveness thresholds related to severity, burden of illness, or "need."", including for rare diseases[217].

- **Stakeholder engagement**

AHRQ reports that "Clinical and content experts" and sometimes patients inform "prioritisation and selection of harms" for systematic reviews [219]. Topics for systematic review are informed by "patients, consumers, advocacy organisations, clinicians, researchers, agencies that issue guidelines, policymakers, industry, or health care organisations", and the draft protocol is made public for comment [220]. Stakeholders similar to the above are convened to discuss the review results [218]. Patient-Centered Outcomes Research Institute (PCORI) "engages patient and stakeholder partners in a variety of ways—serving on working groups or advisory committees, developing dissemination strategies, or engaging in study design and execution". The Advisory Committee on Immunisation Practices (ACIP) "works closely with external stakeholder groups, including physicians; their meetings are open to the public and include open discussion and public comment" [7, 219].

The Institute for Clinical and Economic Review's (ICER) standard review timeline begins stakeholder outreach at the outset of topic selection: "ICER notifies relevant stakeholders and begins scoping calls with patient groups, clinical experts, manufacturers, payers to inform the draft scope for the assessment" [221]. There are then public comment windows, first on the draft scoping document and then for 20 days after the draft evidence report is produced. A public meeting is then held prior to the final report being produced. Industry has several opportunities to provide data during assessment. One study identified 463 comments within the 55 letter submissions identified across the 7 included ICER reviews [222]:

> Drug manufacturers (63.1%), patients or patient advocacy groups (18.1%), and providers or provider groups (9.7%) were the stakeholders most often engaged in the public comments. The comments most often addressed the methodology of the value assessment (53.8%). Comments about missing data (14%), general criticism (8.2%), and general support (2.2%) were less common [222].

- **Special Pathways**

There is no special pathway for reimbursement of first-in-class drugs in the US, however, the FDA has increasingly approved novel drugs that fulfill an unmet clinical need through expedited review pathways such as fast track; breakthrough therapy; priority review and accelerated approval. Though these pathways are not limited to fist-in-class or novel drugs, however, data indicated that 74% of novel drugs were approved through one of these pathways in 2021 [223]. Similarly, there is currently no specific pathway for coverage decisions for high-cost treatment. The Drug covered under Medicare Plan D can have conditional coverage or limited coverage depending upon the availability of evidence or budget impact, however, Medicaid coverage policies limit the state's authority to limit or negotiate rebates with manufacturers specifically for high-cost treatment which mostly get market approval through FDA expedited pathways. The states are required to provide coverage for all the drugs approved by the FDA and included in the MDRP [224].

In 2014, the FDA issued its guidance for the co-dependent technologies to help companies plan for co-development of companion diagnostic tests (CDx) and medicines. There are two pathways provided in this guidance document for approval of drug and companion diagnostic test: one where the companion diagnostic test is developed and approved at the same time the medicine is developed and submitted to the FDA for market approval; second where the FDA can approve the novel drug for which the CDx is not yet approved. In the second scenario, the FDA expects that the CDx will be subsequently submitted and approved and considers the safety issues of the drug in the absence of CDx [225]. Recently, the FDA also issued guidance for its pilot program to provide transparency in specifying the performance characteristics of CDx to be used to identify patients for certain oncology drug treatments [226].

For certain antibiotics, the FDA can grant a 'qualified infectious disease product' (QIDP) designation under Generating Antibiotic Incentives Now (GAIN) Act of 2012. Through this designation, some antimicrobials can have five additional years of market exclusivity as well as expedited approval through fast-track review. This expedited approval with market exclusivity is only for antimicrobials that target a certain list of 'qualifying pathogens' or treat drug-resistant pathogens [227].

Medicines that are granted the designation of orphan drugs qualify for certain incentives such as exemption from user fees, tax credits for qualified clinical trials and market exclusivity for seven years. However, orphan drugs go through the same review process as any other drug for approval but can be considered under expedited pathways depending upon the clinical need. The FDA definition of an orphan drug aimed to treat a rare disease that affects fewer than 200,000 people in the US or in cases where it affects more than 200,000 people, there is no reasonable expectation that manufacturing cost can be recovered. Orphan drugs are usually covered under Medicare Plan D, Medicaid MRDP or paid through self-finance (out-of-pocket payments or private insurance plans). Medicare Plan D for small-group drugs usually provides coverage for drugs that are the only products available in a specific class. This is the case with most orphan drugs; therefore, they qualify for coverage through the Medicare D plan.

Similarly, Medicaid MDRP provides coverage for many orphan drugs targeted for ultra-rare disease, however, it varies from state to state [228].

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