Health Technology Assessment Policy and Methods Review: HTA Methods: Economic Evaluation

Centre for Health Economics Research & Evaluation (CHERE)
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Title: Health Technology Assessment Policy and Methods Review: HTA Methods: Economic Evaluation

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Disclaimer

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The sources used to inform this work contained in were based on information from websites, targeted search of the literature, and expert opinion. The approach we have taken was wide-ranging to identifying the relevant information in the time constraints for delivering this work. It is possible that there is inconsistency between the sources that were used, and some information may have been overlooked or misrepresented.

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Contents

1. HTA methods: Economic evaluation Executive Summary 5

1.1 Background 5

1.2 Methods 5

1.3 Part 1 - Methods in Economic Evaluation 5

1.3.1 Approaches to economic evaluation in Australia and internationally 5

1.3.2 Weighting of health outcomes and risks/harms in Australia and internationally: 9

1.3.3 Welfare impacts of listing a new medicine on the PBS 20

1.3.4 Extrapolation and discounting in Australia and internationally+ (CHERE Discount rate review paper) 22

1.3.5 Assessment of economic uncertainty in Australia and internationally 24

1.4 Part 2 - Special considerations for particular technology of populations types and sizes 25

1.4.1 Rare diseases and small patient populations 25

1.4.2 High unmet clinical need and equity considerations 26

1.4.3 Co-dependent technologies 27

1.4.4 New and emerging technologies 28

1.4.5 Multiple small populations/sub-groups, and flow-on effects for pricing 29

1.5 Part 3: Recent reforms to economic evaluation processes and methodology in Australia and internationally 30

2. Background 32

HTA in Australia 32

3. Purpose and structure of the paper 40

4. Methods 42

4.1 Website searches 42

4.2 Targeted literature searches and grey literature 42

4.3 Stakeholder interviews 43

5. Findings Part 1: Methods in economic evaluation 45

Approaches to economic evaluation in Australia and internationally 45

HTA systems globally 45

Perspectives 45

Systematic review of economic evaluations 46

Selection of comparators 46

HTA approaches to economic evaluation across jurisdictions 51

Health technology claims of no difference 54

Health technology claims of a substantial improvement 62

Conclusion 63

Weighting of health outcomes and risks/harms 65

a. Weighted scales 66

b. Patient-relevant outcomes including PROMs and PREMs. 79

c. Consideration of patient preferences 86

d. Indirect and non-health benefits and harms 92

Welfare impacts of listing a new medicine on the PBS 103

Extrapolation and discount rates 105

Comparisons of methods across jurisdictions 106

Time horizon 108

Reproducing time-to-event from published sources 113

Model selection 113
Assessment of economic uncertainty in Australia and internationally 118
Methodological uncertainty 118
Structural uncertainty 119
Parametric uncertainty 119

6. Findings Part 2: Special considerations for particular technology of populations types and sizes 124

Rare diseases and small patient populations 124
Definitions 125
Comparisons of HTA methods and processes across jurisdictions 125
Special considerations for economic evaluation/processes 128
High unmet clinical need and equity considerations 139
High unmet clinical need 139
Health equity 139
Assessing health equity in HTA 140
Vulnerable and disadvantaged populations 140
Quantifying health equity impacts 140
Conclusion 141
Co-dependent technologies 141
Comparisons of methods and processes across jurisdictions 143
Evidence requirements 144
HTA process 145
Conclusion 148
New and emerging technologies 148
Definition: Surrogate outcome 150
Comparisons of surrogate outcomes 150
Comparisons of methods and processes across jurisdictions 153
Published peer-reviewed literature 160
Conclusion 165
Separate or combined consideration of multiple small populations/sub-groups, and flow-on effects for pricing. 166
Comparisons of methods and processes across jurisdictions 166
Methodologies for flow on pricing from the literature 167
Conclusion 170

7. Findings Part 3: Recent reforms 172

Recent changes to economic evaluation processes and methodology in Australia and internationally 172
a. Processes and the alignment with health technologies 172
b. Outcomes of reforms 172

8. Appendix 178

Appendix 1: Relevant sources 179

Appendix 2: Consolidated interview protocol 182

References 186

Abbreviations

ACE	Agency for Care Effectiveness (Singapore)
ACPM	Advisory Committee on Prescription Medicines (Australia)
AE	adverse events
AEMPS	Spanish Agency of Medicines and Medical Devices
AETS	Agencia de Evaluación de Technologias Sanitarias (Spain)
AHP	Analytic hierarchy process
AIC	Akaike information criterion
AQoL	Assessment of Quality of Life instrument
ARCS	Association for Regulatory and Clinical Scientists (Australia)
ARTG	Australian Register of Therapeutic Goods
AS	absolute shortfall
ASMR	Amelioration du Service Medical Rendu (French High Authority of Health Scale)
ATAGI	Australian Technical Advisory Group on Immunisation
ATMP	advanced therapy medicinal products
BHM	Bayesian hierarchical modelling
BIC	Bayesian information criterion
C2H	Center For Outcomes Research And Economic Evaluation For Health (Japan)
CA	conjoint analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CAGs	Clinical Advisory Groups
CAHIAQ	Catalan Agency for Health Information, Assessment and Quality (Spain)
CatSalut	Catalan Health Service (Spain)
CBA	cost-benefit analysis
CCA	cost-consequence analysis
CDE	Center for Drug Evaluation (Taiwan)
CEA	cost-effectiveness analyses
CEE	Central and Eastern European countries
CEESP	Commission for Economic Evaluation and Public Health
CEPS	Economic Committee for Health Products (France)
CHERE	Centre for Health Economics Research and Evaluation
CHTE	Centre for Health Technology Evaluation
CHU9D	Child Health Utility instrument
CMA	cost-minimisation analysis
CUA	cost-utility analyses
DCE	Discrete choice experiment
DCEA	Distributional cost-effectiveness analysis
DoHAC	Department of Health and Aged Care
DRD	Drugs for Rare Disease
DSA	deterministic sensitivity analyses
DSU	Decision Support Unit (England & Wales)
DUSC	Drug-Utilisation Sub-Committee (Australia)
EAMS	Early access to medicines scheme
ECAG	Expert Clinical Advisory Groups (Australia)

EMA	European Medicines Agency
ESC	Economics Sub-Committee (Australia)
EUnetHTA	European Network of Health Technology Assessment
FCA	friction cost approach
FDA	US Food and Drug Administration
FTA	Fast-track approval
G-BA	Federal Joint Committee (Germany)
GBMA	Generic and Biosimilar Medicines Association (Australia)
HAS	Haute Autorité de Santé (French National Authority for Health)
HATV	High Added Therapeutic Value
HCA	human capital approach
HIRA	Health Insurance Review and Assessment Service (South Korea)
HPA	Health Promotion Administration (Taiwan)
HRQoL	health-related quality of life
HST	Highly specialised technologies
HTA	health technology assessment
HTAA	Health Technologies Assessment Agencies (Spain)
HTAi	Health Technology Assessment International
HUI	Health Utilities Index
ICC	Intracohort Comparison
ICER	incremental cost-effectiveness ratio
ICER-US	Institute for Clinical and Economic Review (US)
INESSS	Institut National d'Excellence en Santé et Services Sociaux (Canada, Quebec)
IPD	individual patient data
IQWiG	Institute for Quality and Efficiency in Health Care (Germany)
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
JCVI	Joint Committee on Vaccination and Immunisation (UK)
KCE	Health Care Knowledge Centre (Belgium)
LSDP	Life Saving Drugs Program (Australia)
LYG	Life years gained
LYSARC	Lymphoma Academic Research Organisation (France)
MA	Medicines Australia
MAIC	matched-adjusted indirect comparisons
MAUI	multi-attribute utility instruments
MBS	Medicare Benefits Schedule (Australia)
MCDA	multi-criteria decision analysis
MCID	minimal clinically important difference
MDHTAC	Medical Devices and Human Tissue Advisory Committee (Australia)
MEA	Managed Entry Agreement
MEB	Medicines Evaluation Board
MES	Managed Entry Scheme
MHLW	Ministry of Health Law and Welfare (Japan)
MHRA	Medicines and Healthcare products Regulatory Agency (Scotland)
MoH	Ministry of Health (Singapore)
MPC	Molecular Pathology Consortium (Scotland)
MRFF	Medical Research Futures Fund
MSAC	Medical Services Advisory Committee (Australia)
MTA	multiple technology appraisal

MTAA	Medical Technology Association of Australia
MTAC	Medical Technology Advisory Committee (Singapore)
MTEP	Medical Technologies Evaluation Programme (England & Wales)
NA	Not Applicable
NBA	National Blood Authority (Australia)
NDC	New Drugs Committee (Scotland)
NDIS	National Disability Insurance Scheme
NECA	National Evidence-based healthcare Collaborating Agency (South Korea)
NHS	National Health Service (England & Wales)
NHSScotland	National Health Service (Scotland)
NICE	National Institute for Health and Care Excellence (England & Wales)
NIHA	National Health Insurance Administration (Taiwan)
NIHR	National Institute for Health Research (UK)
NIHTA	The National Institute for Health Technology Assessment (Taiwan)
NIPH	Norwegian Institute of Public Health
NIP	National Immunisation Program (Australia)
NOK	Norwegian Kroner
NOKC	Norwegian Knowledge Centre for the Health Services
NoMA	Norwegian Medicines Agency
NPAF	New Product Assessment Form
NPF	Nordic Pharmaceutical Forum
NPWP	Nutritional Products Working Party (Australia)
OHE	Office of Heath Economics (UK)
OS	Overall survival
PAS	Patient Access Scheme
PASC	PICO Advisory Sub-Committee (Australia)
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
PBCAC	Pharmaceutical Benefit Coverage Assessment Committee (Australia)
PBS	Pharmaceutical Benefits Scheme (Australia)
pCODR	Pan-Canadian Oncology Drug Review
PDC	Prosthesis and Devices Committee
PE	pharmacoeconomic
PFPA	Prescription for Pharmacoeconomic Analysis (New Zealand)
PFS	progression-free survival
PHARMAC	Pharmaceutical Management Agency (New Zealand)
PICO	population, intervention, control, and outcomes
PLAC	Prostheses List Advisory Committee (Australia)
PoCE	Panel of Clinical Experts (Australia)
PROM	patient-reported outcome measure
PRO	patient-reported outcome
PREM	patient-reported measure
PS	proportional shortfall
PSA	probabilistic sensitivity analyses
PSD	Public Summary Document (Australia)
PSM	partitioned survival model
PTAC	Pharmacology and Therapeutics Advisory Committee (New Zealand)
QALY	Quality adjusted life years
QoL	Quality of life

QUOKKA	Quality of Life in Kids: Key Evidence in Australia Research Program
QWB	Quality of Well-being scale
RCT	randomised controlled trial
RIZIV -INAMI	National Institute for Health and Disability Insurance (Belgium)
RSA	Risk Share Agreement
RWE	real-world evidence
SF-36	36-Item Short Form Survey
SF-6D	Short Form 6-Dimension Survey
SG	standard gamble
SLR	systematic literature review
SMA	spinal muscular atrophy
SMC	Scottish Medicines Consortium
SO	surrogate outcome
SPA	Special Pricing Arrangement
SPaN	Scottish Pathology Network
STA	Single technology appraisal (England & Wales)
TFDA	Taiwanese Food and Drug Administration
TGA	Therapeutic Goods Administration (Australia)
TLV	Dental and Pharmaceutical Benefits Agency (Sweden)
TSD	Technical Support Documents (England & Wales)
TTO	time-trade off
UK	United Kingdom
US	United States of America
UTS	University of Technology Sydney
WHO	World Health Organization
WTP	willingness-to-pay
ZIN	Zorginstituut Nederland (National Health Care Institute, Netherlands)

1. HTA methods: Economic evaluation Executive Summary

1.1 Background

This paper provides an overview of the methods used in economic evaluation as part of health technology assessment (HTA) processes in Australia and other jurisdictions of interest where HTA is used to support reimbursement for new health technologies. Based on guidance provided by the HTA Review Reference Committee, the jurisdictions of interest considered in this paper were the United Kingdom (UK) (England and Wales; Scotland), Canada, New Zealand, France, Germany, Norway, Spain, Sweden, the Netherlands, Belgium, Luxembourg, Japan, South Korea, Singapore, and Taiwan. Methods from other jurisdictions were considered if relevant to the Australian Health System.

The paper is structured in three parts, describing: the methods used in economic evaluation (Part 1); special considerations for particular technologies and for specific populations (Part 2); recent reforms and changes to economic evaluation processes and methods (Part 3).

1.2 Methods

Information pertaining to economic evaluation methods were gathered from several sources, including; websites of national/jurisdictional HTA agency and HTA organisations and societies, published literature, and interviews with key stakeholders. A comparative framework of economic evaluation methods used across jurisdictions was used to evaluate the similarities, differences and relevance to the Australian setting of those cross-country practices.

1.3 Part 1 - Methods in Economic Evaluation

1.3.1 Approaches to economic evaluation in Australia and internationally

1.3.1.1 HTA systems globally

Economic evaluation provides a framework to systematically compare interventions so that all relevant alternatives are clearly identified, analysed and evaluated. The extent to which HTA processes rely on the results from economic evaluations for (reimbursement) decision-making differs across jurisdictions. Twelve of the jurisdictions included within this review formally apply economic evaluations in decision-making (Australia; England and Wales; Scotland; New Zealand; Canada; The Netherlands; Belgium; Norway; Sweden; Singapore; South Korea; Taiwan). Japan

only formally uses economic evaluation as part of drug price reviews in cases where price premiums are considered. In France, HTA processes are primarily used for price setting and not reimbursement; the Haute Autorité de Santé (HAS) (French National Authority for Health) specifies cases where economic evaluation will be required for drugs and devices. Two jurisdictions, Germany and Spain, do not use economic evaluations for decision-making.

1.3.1.2 Perspectives

Three jurisdictions (the Netherlands (ZIN); Taiwan (CDE); Sweden (TLV)) state the societal perspective is used in economic evaluation for the reference case[1]; for all other agencies, the healthcare payer perspective is considered for the reference case. This differentiation in perspective results in different methods being considered by the Netherlands, particularly relating to inclusion of costs and benefits in economic modelling.

1.3.1.3 Selection of comparators

HTA is essentially a comparative assessment: In order to make an assessment of the impact of a health technology on the health of patients the technology must be compared to existing technologies. The choice of comparator affects the assessment of comparative costs and outcomes and therefore the claims for a technology (e.g., of superior clinical outcomes, justifying a higher price) will depend on the comparator(s) nominated and the type of evidence presented.

In Australia, the recommended comparator in the PBAC and MSAC Guidelines is the alternative that is most likely to be replaced with the introduction of the new intervention. The same recommended comparator is also applied by the National Institute for Health and Care Excellence (NICE) in England and Wales, the Scottish Medicines Consortium (SMC), the Canadian Agency for Drugs and Technologies in Health (CADTH), the Pharmaceutical Management Agency (PHARMAC) in New Zealand, the Norwegian Medicines Agency (NoMA), the Center For Outcomes Research And Economic Evaluation For Health (C2H) in Japan, the Agency for Care Effectiveness (ACE) in Singapore, and the Center for Drug Evaluation (CDE) in Taiwan.

However, in Australia, if the requested listing costs more than the alternative, the PBAC can only recommend if it is satisfied that the treatment provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953*, Section 101(3B)). The PBAC must provide a statement it is satisfied

[1] A reference case gives a formal statement of accepted methods and assumptions underpinning analyses to which submissions should conform. See Section under 'Assessment of economic uncertainty in Australia and internationally'.

that this condition has been met in its recommendation. In practice this means that alternative therapies that are not the therapy most likely to be replaced may be relevant to the assessment for the purposes of pricing.

1.3.1.4 HTA approaches to economic evaluation across jurisdictions

A summary of the approaches to economic evaluation discussed in the guidelines of the selected HTA agencies is presented in Table 1.

Table 1 Summary of preferred methods used for decision-making based on clinical claims across HTA agencies

Jurisdiction	Agency	Claims: Substantial improvement in efficacy or reduction in toxicity compared to alternatives?		Use of cost-effectiveness thresholds
		No claim	There is a claim	
Australia	PBAC and MSAC	CMA [a]	CUA (preferred) CEA CCA (supportive) [b]	No
England and Wales	NICE	CMA/Cost comparison Faster process	CUA (preferred) CEA CCA (supportive) [b]	Yes
Scotland	SMC	CMA Faster process	CUA (preferred) CEA CCA (supportive) [b]	No
Canada	CADTH	CEA/CUA CMA (supplementary only where certain conditions are met)	CUA (preferred) CEA	No
New Zealand	PHARMAC	CMA	CUA (preferred) CEA	No
France	HAS	Assessment of added benefit	Preference unspecified: CUA, CEA; Assessment of added benefit	No
Germany	IQWiG/G-BA	Assessment of added benefit	Assessment of added benefit	No
Norway	NOMA/NIPH	CMA	CUA (preferred) CEA	Yes
Sweden	TLV	CMA	CEA, CUA	No
The Netherlands	ZIN	CMA	CEA, CUA	Yes
Belgium	KCE	CEA/CUA is used to show health outcomes are identical prior to CMA being considered appropriate	CEA, CUA	Unclear
Spain	Various	Unclear	Unclear	No
Japan	C2H	CMA	Preference unspecified: CUA, CEA.	No
South Korea	NECA	Unclear	Preference unspecified: CUA, CEA.	No
Singapore	ACE	CMA Faster process	CUA (preferred) CEA	No
Taiwan	NIHTA or CDE	CMA	Preference unspecified: CUA, CEA.	No

ACE = Agency for Care Effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CCA = cost-consequence analysis; CDE = Center for Drug Evaluation (Taiwan); CMA = cost-minimization analysis; CUA = cost utility analysis; G - BA = Gemeinsamer Bundesausschuss (The Federal Joint Committee, Germany); HAS = French National Authority for Health; HTA = Health Technology Assessment; IQWiG =

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Gremany); KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee (Australia); NECA = National Evidence-based healthcare Collaborating Agency (South Korea); NICE = National Institute for Health and Care Excellence (England and Wales (NICE)); NIHTA = The National Institute for Health Technology Assessment (Taiwan); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); UK= United Kingdom; ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).
There was no information pertaining economic evaluation approaches used formally by Spain.
Luxembourg does not have a formalised process for HTA.
a The PBAC guidelines refer to 'cost-minimisation approach', but is referred to as 'cost-minimisation analysis' for this report.
b Cost consequence analysis (CCA) only used in the assessment of medical technologies by MSAC and NICE; and considered for ultra-orphan medicines by SMC. It is recommended that CCA is presented as a supplementary analysis.
Source: PBAC guidelines 2016 [1]; MSAC guidelines 2021 [2]; NICE guidelines 2022 [3]; SMC guidelines 2018 and 2022 [4, 5]; CADTH guidelines 2017 [6]; PHARMAC guidelines 2015 [7]; EUNetHTA guidance document 2015 [8]; HAS guidelines 2020 [9]; IQWiG guidelines 2022 [10]; NoMA (pharmaceuticals) guidelines 2018 [11]; NoMA (medical devices and diagnostic interventions) guidelines 2021 [12]; ZIN guidelines 2016 [13]; KCE guidelines 2012 [14]; C2H guidelines 2022 [15]; HIRA guidelines (Bae et al.) 2022 [16]; ACE (medical technologies) guidelines 2022 [17]; ACE (drug and vaccine) guidelines 2021 [18]; CDE (TasPOR) guidelines 2006 [19].

England and Wales, Norway, and the Netherlands have explicit cost-effectiveness thresholds for decision-making in healthcare resource allocation. While Australia has guidelines for considerations of cost-effectiveness, there is not an explicit threshold that must be met for new interventions to be recommended by PBAC or MSAC.

1.3.1.5 Health technology claims of no difference

Several guidelines for HTA recommend cost-minimisation analysis (CMA) as the main approach to use where no substantial improvement in efficacy or reduction in toxicity is claimed compared to the alternative (herein termed 'non-inferior'): Australia, PBAC and MSAC; UK NICE; New Zealand, PHARMAC; Norway, NoMA and NIPH; Scotland, SMC; Sweden, TLV; France, HAS; Taiwan; Singapore, ACE; Japan, C2H; South Korea, HIRA.

The current approach used in Australia for pricing of health technologies claiming non-inferiority is consistent with cost-equivalence rather than cost-minimisation; where cost-equivalence refers to net costs being maintained (i.e., at the same level), and cost-minimisation refers to the net costs being lower than associated with the comparator. The PBAC and MSAC guidelines state (PBAC Guidelines 2016, v5.0 p100; MSAC Guidelines 2021, v1.0 p205) that at the price requested, the overall cost of therapy with the proposed medicine should be the same as, or less than, the overall cost of therapy with the main comparator. PHARMAC in New Zealand is one agency that practices cost-minimisation in their HTA processes. The PHARMAC guidelines states (PHARMAC Prescription for Pharmacoeconomic Analysis, 2015 p8), CMA assumes there is no net health change involved in moving from one treatment to another, so the decision is made on the basis of the difference in total cost alone. PHARMAC also conduct activities to support cost-minimisation including tendering processes and use of multi-product agreements [20].

Two agencies have a faster process for the assessment of products claiming non-inferiority compared with treatments claiming a substantial improvement (UK, NICE; Singapore, ACE). The faster process is used for drugs in the same therapeutic class or with a change in formulation, and are subject to budget impact and cost-effectiveness thresholds. ACE in Singapore conduct expedited evaluations for products claiming non-inferiority, of 2 to 3 months in duration (for products claiming superiority, evaluations are estimated to take between 6 to 9 months, and for vaccines the estimated timeframe is 6 to 12 months). In Singapore, reimbursement committee recommendations precede financing approval. NICE have outlined two different methods using a proportionate approach including: 1) cost comparison appraisals; and 2) streamlined decision-making - for technology appraisals that are beyond those suitable for cost comparison. The NICE Guidelines (2022) stipulate that it is not possible to set absolute timelines for all stages of the evaluation.

In Australia, all new drug submissions are evaluated by the PBAC within a 17-week cycle. This means that drug products claiming non-inferiority are processed using the same timelines as products claiming superiority. However, the time from first submission to PBS listing can be significantly longer than 17 weeks, as the evaluation cycle does not include the potential resubmission of evidence and modelling if a recommendation to list does not ensue. In addition to this time, the finalisation of pricing and budget impact is conducted with the applicant and the Department of Health and Aged Care (DoHAC) after the PBAC has recommended the medicine for listing [21].

1.3.1.6 Health technology claims of substantial improvement

For health technologies that claim superiority i.e., substantial improvement in efficacy or safety for the technology compared to alternatives, the preferred economic evaluation approaches are cost-effectiveness analyses (CEA) and cost-utility analyses (CUA). The approach taken by Australia is consistent with most agencies, where the perspective of the analysis is that of the health care funder and there is a reliance on CUA/CEA to inform cost-effectiveness for health technologies.

1.3.2 Weighting of health outcomes and risks/harms in Australia and internationally:

Various methods have been used to assess the trade-offs between health outcomes and risks/harms of interventions. In this section, how those trade-offs and weights have been determined and applied in HTA in relation to health outcomes and risks/harms is discussed, with a focus on the use of weighted scales, patient relevant outcomes, patient preferences, and

indirect and non-health benefits. A summary of the methods applied across jurisdictions for the weighting of health outcomes and risk/harms is provided in Table 2.

Table 2 Methods for weighting of health outcomes and risks/harms

Method	Point of application within HTA		Comments/reasons for application
	Decision-making process	Modelling	
MCDA	Yes: committee deliberation	No	Also referred to as Analytic Hierarchy Process used in Germany.
Conjoint analysis DCE MAUI	 Possible Possible	 Possible Yes	DCE methods are discussed in the literature with possible applications in HTA.
TTO	No	Yes	Utility weights used in modelling
SG	No	Yes	Utility weights used in modelling
QALY weighting	No	Yes	Shortfall method e.g., severity modifier. Used by England and Wales (NICE), Norway (NoMA and NIPH), The Netherlands (ZIN). Caregiver e.g. Sweden (TLV)
Friction cost approach (FCA)	No	Yes	Economic evaluation using societal perspective
Human capital approach (HCA)	No	Yes	Economic evaluation using societal perspective

DCE = Discrete Choice Experiment; FCA = Friction cost approach; HCA = Human capital approach; HTA = Health Technology Assessment; MAUI = multi-attribute utility instruments; MCDA = multicriteria decision analysis; NICE = National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; QALY = quality adjusted life year; SG = Standard Gamble; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); TTO = time trade-off; ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).

The most widely approach in the economic evaluation framework is to value health benefit using quality adjusted life years, in which all health benefits are valued on the same scale regardless of the recipient. This approach has been criticised for neglecting societal preferences that may prioritise certain individual groups health gains over others, thereby overlooking considerations of equity [22] [23]. In response to this debate, different approaches have been suggested for operationalising the equity-efficiency trade-off [22] [24]. Currently, value assessment frameworks used by HTA agencies, account for the various aspects of social values implicitly and/or explicitly (see section Part 1 Weighting of health outcomes and risks/harms). Value has been defined as both therapeutic benefits of a technology for patients and their broader social impact [25].

1.3.2.1 Weighted scales

Methods described for weighting health outcomes and risks/harms include multi-criteria decision analysis (MCDA), and stated preference methods including conjoint analysis and discrete choice experiments (DCEs). These methods allow relative weights to be assigned to different health outcomes and health care services to reflect their importance for societal impacts and resource allocation.

The methods and processes for the weighting of outcomes discussed in the HTA guidelines and websites across the jurisdictions of reference are presented in Table 3.

Table 3 Consideration of weighting of decision factors across jurisdictions and HTA agencies

Jurisdiction (HTA agency)	Mentioned in the guideline	Method used for weighting of decision factors	Application
Australia (PBAC, MSAC)	No (not explicitly)	Qualitative deliberation: In making recommendations the PBAC/MSAC apply judgements to value health technologies during deliberation.	PBAC does not explicitly apply weighing to health outcomes in economic modelling. However, other less-readily quantifiable factors that also influence PBAC decision-making are outlined (PBAC Guidelines v5.0 pp4-5). [Consultation – consumer/patient groups; Submission can provide additional evidence in the form of expert opinion (PBAC Guidelines v5.0 Appendix 1)].
England and Wales (NICE)	Yes	Structured deliberation: MCDA applied with decision rules. (1) MCDA (2) Decisions modifiers; proportional shortfall and absolute shortfall	MCDA: To support cost–consequences analysis when a cost per QALY approach is not possible Decision modifiers (severity and size of benefit): When QALYs do not factor in all benefits, because they cannot be, and value judgements. Modifiers can be taken into account qualitatively through committee discussion or quantitatively.
Scotland (SMC)	No (not explicitly)	Qualitative deliberation.	SMC do not explicitly apply weighing to health outcomes. However, other factors are considered that can also influence decision-making. An additional QALY is of equal value regardless of individual characteristics such as their socio-demographic details, or their pre- or post-treatment level of health end-of-life/rare medicines.
Canada (CADTH)	Not explicitly specified	Qualitative deliberation. In the reference case, all health outcomes should be weighted equally, regardless of the characteristics of people receiving, or affected by, the intervention in question	However, it allows for weighting of health outcomes to consider distributional and equity-related policy concerns.
New Zealand (PHARMAC)	No (not explicitly)	Qualitative deliberation. Health-related benefits included in a cost-utility analysis should not be weighted	PHARMAC do not explicitly apply weighing to outcomes in economic modelling. Factors outlined for consideration for decision-making by PHARMAC are: need, health benefits, suitability, and costs and savings.
France (HAS)	No	-	Weighting of QALYs according to the individual characteristics of the persons involved in the intervention (socio-demographic factors, severity, etc.) is not recommended.
Germany (IQWiG)	Yes	Quantitative deliberation: Analytic hierarchy process (AHP) and discrete choice experiments (DCE).	Determination of preferences to establish a measure of overall benefit.
Norway (NIPH/NoMA)	Yes	QALY weighting	Factors considered: equal access, need, and solidarity, aiming to ensure fairness and equity in resource allocation.

Jurisdiction (HTA agency)	Mentioned in the guideline	Method used for weighting of decision factors	Application
		Similar to NICE, according to absolute shortfall of QALYs. Variable threshold.	For prevention and severe diseases.
Sweden (TLV)	Yes	QALY weighting using severity (note: severity is not clearly defined) Variable threshold.	Caregivers QoL included in economic evaluation (reference case for ATMPs,). Principles of human dignity, need, cost-effectiveness, and solidarity, allocating resources based on need and considering factors such as illness severity, patient preferences, and societal values alongside cost-effectiveness.
The Netherlands (ZIN)	Yes	DCE and MCDA (directly consulting patients and users). References the NICE Diag Assessment Programme. Proportional shortfall method. Variable threshold.	Principles of human dignity, need, cost-effectiveness, and solidarity, allocating resources based on need and considering factors such as illness severity, patient preferences, and societal values alongside cost-effectiveness. In Netherland for diagnostic test to identify other value components (which were not specified in the guidelines)
Singapore (ACE)	No (not explicitly)	Qualitative deliberation: In making recommendations the committees apply judgement to value health technologies.	ACE does not explicitly apply weighting to health outcomes in economic modelling. Factors outlined for consideration for decision-making by the committees are: Clinical need of patients, clinical effectiveness, safety and cost-effectiveness of the technology, and budget impact. Additional factors, including social, cultural and ethical issues, and other value judgements may also inform their considerations.

ACE= Agency for Care Effectiveness; AHP= Analytic hierarchy process; ATMPs= Advanced therapy medicinal products; CADTH= Canadian Agency for Drugs and Technologies in Health; DCE= Discrete choice experiment; HAS= Haute Autorité de Santé; HTA= Health technology assessment; MCDA= Multicriteria decision analysis ; MSAC= Medical and Scientific Advisory Council; NECA= National Evidence-based healthcare Collaborating Agency; NICE= National Institute for Health and Care Excellence; NIPH= Norwegian Institute of Public Health; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; QALY= Quality adjusted live year; SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; UK= United Kingdom; ZIN= The National Health Care Institute.

There was no information pertaining to the use of weighting of decision factors specified by these jurisdictions (Belgium; Luxembourg; Spain; Japan; South Korea; Taiwan).

Source: ACE guidelines 2023; C2H guidelines 2022; CADTH guidelines 2017; HAS guidelines 2020; IQWiG guidelines 2022; KCE guidelines 2012; MSAC guidelines 2021; NICE guidelines 2022; NoMA guidelines 2018; PBAC guidelines 2016; PHARMAC guidelines 2022; SMC guidelines 2022; TLV guidelines for precision medicine 2022 and ZIN guidelines 2016.

There are challenges that arise when using stated preference methods for the weighting of decision factors. Developing a set of weights acceptable for decision-making may be problematic where flexibility in the decision-making process is needed, particularly for where there are important differences in values relating to health outcomes and other factors considered in decision-making.

In the HTA guidelines of relevant jurisdictions, three general approaches to the weighting of health outcomes have been identified. One of these approaches applies equity weights to QALY gains and evaluates the adjusted incremental cost-effectiveness ratio (ICER) against a fixed

monetary threshold value (England and Wales (NICE)), and another evaluates an unadjusted ICER against a flexible monetary threshold value (Norway (NoMA) and The Netherlands (ZIN)).

A third approach is qualitative deliberation where no explicit weighing of QALYs is done (i.e. Australia (PBAC, MSAC)). In this regard, New Zealand (PHARMAC) states that HTA is a deliberative process informed by quantitative models, but they are not deterministic. Decision makers can choose how much and how to weight quantitative and qualitative results to arrive at a decision.

1.3.2.2 Severity of a health condition and QALY weighting

Four jurisdictions (England and Wales (NICE); The Netherlands (ZIN); Norway (NIPH); Sweden, (TLV)) have operationalised the weighting of QALYs by including severity as one of the factors to consider in the decision-making process. The estimation of severity of a health condition involves using the concept of QALY shortfall in the Netherlands (ZIN), Norway (NIPH/NoMA), and the England and Wales (NICE). However, the approach to defining severity differs between these jurisdictions.

- Absolute Shortfall (AS) score: represents the number of future QALYs lost by individuals living with a particular disease. Using this approach means younger patient populations have a higher number of potential future QALYs to lose on average. As a result, chronic diseases affecting younger populations may receive higher AS scores compared to severe acute diseases that primarily affect older populations.
- Proportional Shortfall (PS) score: represents the proportion of future QALYs lost by individuals living with the disease. Older or elderly patient populations, who are closer to the end of their lives, have relatively fewer potential QALYs left on average. Consequently, they are more likely to lose a higher proportion of their remaining QALYs due to a severe disease, leading to higher PS scores on average.

Table 4 Comparison of QALY weighting across the Netherlands (ZIN), Norway (NIPH/NoMA) and England and Wales (NICE)

Criteria	Netherlands (ZIN)		Norway (NIPH/NoMA)		England and Wales (NICE)	
	Proportional Shortfall (PS) (QALY)	Threshold (€/QALY)	Absolute Shortfall (AS) (QALY)	Threshold (NOK/QALY)	Shortfall (PS and AS) (QALY)	QALY weight
Proportional Shortfall						
Low	0.1–- 0.4	Up to 20,000			<0.85	x1
Medium	0.41–- 0.7	Up to 50,000			0.85–- 0.95	x1.2
High	>0.71	Up to 80,000			>0.95	x1.7
Absolute Shortfall						
Low			0– 15	<250,000	<12	x1
Medium			16– 30	<500,000	12 – 18	x1.2
High			31– 45	<750,000	≥18	x1.7

Source: Guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. 2018. NoMA, Norway; Guideline for economic evaluations in healthcare. 2016. ZIN, Netherland and NICE health technology evaluations: the manual. Process and Methods. 2022.

In Sweden, the TLV's approach does not rely on using the QALY shortfall due to the influence of the Human Dignity Principle and the TLV does not have an explicit cost-effectiveness threshold. A review by Barra et al [26] indicated that the TLV approve drugs at a higher cost-effectiveness threshold based on the severity of a condition.

1.3.2.3 Flexibility in the decision-making process

While the use of weighted outcomes can simplify the process of aggregating preferences, there is a risk of overlooking other factors that can be considered using a more flexible decision-making process. A flexible decision-making process enables consideration of various factors beyond estimated health outcomes through qualitative deliberation; where the impact of uncertainty could be considered outside of explicit decision rules. This rigidity in decision-making may impede the ability to adequately address distributive issues and adapt to evolving circumstances. An exclusive reliance on QALYs in the decision-making process (as might be implied for systems which apply a strict ICER threshold) may result in neglecting important distributional considerations in resource allocation decisions. Qualitative deliberation is incorporated into the decision-making process alongside the use of QALYs in some jurisdictions (Australia, PBAC and MSAC; New Zealand, PHARMAC; Canada, CADTH). However, qualitative deliberation can mean that the weight attached to these considerations is not transparent and may not be consistent across decisions.

1.3.2.4 Patient-relevant outcomes including PROMs and PREMs.

Several HTA guidelines referenced the use of validated generic and condition-specific patient-reported outcome measures (PROMs). However, the use of PROMs tends to focus exclusively on the assessment of quality of life, particularly the use of multi-attribute utility instruments (MAUIs) used to derive utility weights for the calculation of QALYs. Stakeholder input to the Review highlighted the importance of PROMs and patient reported experience measures (PREMs) as vehicles for embedding the patient voice within the evidence considered by HTA, facilitating a more patient-centred approach to reimbursement decision-making. A summary of the MAUIs that are recommended or exemplified for use in HTA guidelines is provided in Table 5.

Table 5 HTA guidelines that recommend or encourage the use of a specific MAUI for CUA

	EQ-5D-5L	EQ-5D-3L	SF-6D	HUI (2 or 3)	QWB	AQoL	CHU9D
Specific MAUI(s) recommended							
England and Wales (NICE)	Yes	Yes					

	EQ-5D-5L	EQ-5D-3L	SF-6D	HUI (2 or 3)	QWB	AQoL	CHU9D
Scotland (SMC)	Yes	Yes					
New Zealand (PHARMAC)		Yes					
France (HAS)	Yes						
Norway (NoMA/NIPH)	Yes	Yes					
The Netherlands (ZIN)	Yes						
Belgium (KCE)	Yes	Yes					
Spain (CatSalut)	Yes	Yes	Yes				
Japan (C2H)	Yes						
No specific recommendations but examples provided							
Australia (PBAC/MSAC)	Yes	Yes	Yes	Yes		Yes	Yes
Canada (CADTH)	Yes	Yes	Yes	Yes			
Sweden (TLV)	Yes	Yes					
Spain (HTAA)	Yes	Yes	Yes	Yes			
South Korea (HIRA)	Yes	Yes	Yes	Yes			
Singapore (ACE)	Yes	Yes	Yes	Yes		Yes	
Taiwan (CDE)	Yes	Yes		Yes	Yes		

ACE = Agency for Care Effectiveness (Singapore); AQoL = Assessment of Quality of Life; C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CatSalut = Catalan Health Service (Spain); CDE = Centre for Drug Evaluation (Taiwan); CHU9D = Child Health Utility 9D; HAS = French National Authority for Health; HIRA = Health Insurance Review and Assessment Service (South Korea); HTAA = health Technologies Assessment Agencies (Spain); HUI = Health Utilities Index; KCE = Belgian Health Care Knowledge Centre; MAUI = multi-attribute utility instrument; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); QWB = Quality of Well-Being Scale; SF-6D = Short-Form Six-Dimension; SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); ZIN = Zorginstituut Nederland (National Health Care Institute, the Netherlands).
[There was no information pertaining to the choice of MAUIs specified by Luxembourg (MSS)]
Source:
Guidelines: NICE guidelines 2022; SMC guidelines 2022; PHARMAC guidelines 2015; HAS guidelines 2020; NoMA (pharmaceuticals) guidelines 2018; NIPH guidelines 2021; ZIN guidelines 2016; KCE guidelines 2012; CatSalut guidelines 2014 [27]; C2H guidelines 2022; PBAC guidelines 2016; MSAC guidelines 2021; CADTH guidelines 2017; TLV report 2022; HTAA guidelines (Lopez-Bastida et al) 2010 [28]; HIRA guidelines (Bae et al) 2022; ACE (medical technologies) guidelines 2022; CDE (TasPOR) guidelines 2006

In Australia, the PBAC and MSAC guidelines state that the use of MAUIs other than these measures requires a detailed discussion of the domains, scoring, validity, reliability and responsiveness and minimal clinically important differences (MCIDs). Likewise, the demonstration of good psychometric properties of the selected MAUI is required in several jurisdictions (England and Wales (NICE), Canada (CADTH), Germany (IQWiG), the Netherlands (ZIN), South Korea (HIRA)) and Singapore (ACE). Other considerations are that the selected MAUI should be validated in the country (Australia (MSAC), Germany (IQWiG), Taiwan (CDE)) and in the health condition and intervention (Australia (MSAC)), and should reflect the health states of interest (Canada (CADTH), Germany (IQWiG)).

There appears to be consensus among HTA agencies in terms of the choice of MAUI, with the EQ-5D, HUI and SF-6D cited in most guidelines. Notably, agencies that take a more prescriptive approach provide extensive guidance on alternative methods when the recommended MAUI is deemed inappropriate or unavailable. While there remains ongoing debate about the advantages and disadvantages of recommending a single type of MAUI [29, 30], other agencies

make up for limitations of a broader approach by emphasising the need for well-justified choices accompanied by sensitivity analyses.

Australian guidelines provide key considerations on a range of methodological aspects regarding MAUI selection, use of value sets, and sources of utilities, with no substantial deviation from other guidelines (except that Australia identifies a broader set of recommended MAUIs).

1.3.2.5 Consideration of patient preferences.

A summary of whether patient preferences are considered by HTA agencies is provided in Table 6. There are two main methods for incorporating patient preferences [31-33]:

- Participation: patient preference input refers to the inclusion of patients and/or their representatives in discussions at different stages of the HTA process e.g., committee meetings, calls for written comments, inclusion of patient representatives on advisory groups, testimonials, focus groups, organisation of a patient panel.
- Patient-based evidence: patient preference input refers to the collection of patients'/patient representatives' values and experiences. This includes studies collecting data using a systematic method (e.g., survey, qualitative interviews), where data are analysed for reporting. For example, data collected from patients for valuation of health states to be used in the calculation of QALY weights (e.g., via TTO); or stated preference methods such as a discrete choice experiment (DCE) could be used to examine patient preferences and presented as supporting evidence. Similarly, data collected through qualitative interviews may be informative in setting the context for HTA decision-making or in framing value propositions of otherwise unquantified domains (e.g., impacts on convenience, autonomy, changes in the process of care).

In general, it was found that many jurisdictions consider patient preferences through direct input, which includes patient consultation. This includes Australia (PBAC/MSAC); England and Wales (NICE); Scotland (SMC); Canada (CADTH); New Zealand (PHARMAC); Germany (IQWiG); and Singapore (ACE). There were also a few jurisdictions that explicitly mention consideration of indirect input methods (qualitative or quantitative methods such as conjoint analysis and analytic hierarchy process), such as England and Wales (NICE), Germany (IQWiG), Sweden (TLV), The Netherlands (ZIN) and Japan (C2H).

Patient preferences, captured either through means of participation or use of patient-based evidence, are often used as supporting evidence separate from economic modelling or QALYs. However, there can also be challenges to incorporating patient preferences into the submission or decision-making process. Some challenges raised about incorporating input through participation including tight timeframes [31, 34, 35], additional burden placed on patients [31, 35], difficulty identifying a relevant patient group organisation or specific patients [35], and uncertainty of whether a treatment has met safety standards.

Table 6 Explicit inclusion of patient preference evidence by jurisdiction

Jurisdiction (agency)	Participation	Patient based evidence		Input used:	
		qualitative studies	quantitative studies	As supporting evidence?	In assessment of costs and benefits?
Australia, (PBAC/MSAC)	yes			yes	
England and Wales (NICE)	yes	yes	yes	yes	
Scotland, (SMC)	Yes				
Canada, (CADTH)	Yes			yes	
New Zealand, (PHARMAC)	yes			yes	
Germany, (IQWiG)	yes		yes	yes	yes
Sweden, (TLV)			yes		yes
The Netherlands, (ZIN)			yes		yes
Belgium (INAMI)	yes				
Japan (C2H)			yes		yes
Singapore (ACE)	yes			yes	

Agencies not explicitly stating use of patient preferences through direct or indirect input include: France, HAS Norway, NoMA/NIPH; Spain (various); Belgium, KCE; Luxembourg ; Japan, C2H; South Korea, NECA; Taiwan (NIHA).

Participation is more widely used than patient-based evidence methods as a means of incorporating patient preferences into HTA considerations. A few jurisdictions consider methods using patient-based evidence in their guidelines, namely, Germany, Japan, Sweden and the Netherlands. In particular, Germany has investigated the use of quantitative methods like CA and AHP to capture patient preferences. However, methodological issues have prevented their routine use in German HTA decision-making (see Part 1 Consideration of patient preferences in report for further details).

Australia is similar to many of the jurisdictions reviewed in its acceptance of participant input, as a means of capturing patient preferences. Indeed, consultation with patients and their representatives is very well established in Australia with processes in place for PBAC and MSAC.

1.3.2.6 Indirect and non-health benefits health benefits and harms

The methods and processes used to measure indirect and non-health benefits and harms discussed in the HTA guidelines and websites of the jurisdictions of reference are presented in Table 7.

Table 7 Indirect and non-health benefits and harms methods by country

Jurisdiction	Methods and evaluation approaches	Application
Australia (PBAC, MSAC)	FCA CCA (MSAC) CBA (PBAC) CA or a DCE Impact on carers QoL Value of knowing (MSAC only)	Do not include in the base-case evaluation; Presented as supplementary analyses and outcomes.
England and Wales (NICE)	Method not specified.	Productivity costs should not be included in the reference case. Non health benefits: If substantial proportion of the benefits are associated with significant benefits other than health and only after agreed upon with the Department of Health and Social Care.
Scotland (SMC)	CCA (only for ultra-orphan medicines) Impact on carers QoL (measured using tools such as Carer Experience Scale). Assessment of impact on NHS staffing, infrastructure, and training requirements.	Presented as supplementary analyses and outcomes. Considers impact beyond direct health benefits and on specialist services.
Canada (CADTH)	CCA CBA Non-health effects using time-trade-off or standard gamble. FCA patient and caregiver time for paid labour, and opportunity cost method to estimate productivity costs related to unpaid labour. FCA for productivity losses.	Presented as supplementary analyses and outcomes. Non-health effects considered if the decision problem requires a perspective other than that of the publicly funded health care payer in a non-reference case analysis.
New Zealand (PHARMAC)	Not specified (reasons are given for exclusion of indirect benefits). If indirect health benefits are considered, they should be estimated and discussed in the report as a scenario analysis.	Recommended indirect costs are not included in CUAs. If the treatment might have a measurable but indirect impact on the HR-QoL of others, such as family and caregivers
France (HAS)	HCA or FCA	Health effects are prioritised. Non-health outcomes are not given equal emphasis but can be presented as supplemental analysis
Germany (IQWiG)	FCA HCA	Productivity losses using the FCA with HCA in sensitivity analyses. If the time expenditure of affected persons or relatives is considered, the net wage is used as method to estimate it.
Norway (NoMA, NIPH)	Value of time for caregivers and patients Carer HRQoL quantified in QALYs.	Productivity changes must not be included. If the intervention and the comparator have different time requirements. The costs of the intervention and the comparator must be presented in a way that reflects the differences in time use.
Sweden (TLV)	Including caregivers QoL standardised approximation – a standard rate.	Societal perspective is used for reference case. Only when the impact on family members is high for the condition and the treatment can lead to an improvement in health-related quality of life for the family members.
Belgium (KCE)	HCA. FCA Incremental number of unpaid working days	Include in supplemental analysis if productivity losses, non-health care costs and/or unrelated

Jurisdiction	Methods and evaluation approaches	Application
	Caregivers QoL	health care costs are deemed important for a specific treatment.
The Netherlands (ZIN)	Reference case includes societal perspective including productivity using FCA and costs for patients and families. Intersectoral costs and benefits[a]. Well-being via ICECAP (only for long-term care interventions)	FCA is presented for the reference case using a societal perspective. Intersectoral costs and benefits included for preventive interventions.
Spain (HTAA)	Not specified.	Include cost of labour production losses or lost time. Include cost of caregiver in evaluation when the perspective used requires.
Japan (C2H)	HCA Impact on carer's QoL (no method specified)	Included in supplemental analysis only if this can be estimated using Japanese data.
Taiwan (TaSPOR/ CDE)	HCA	Societal perspective is used for reference case.
Singapore (ACE)	No specific methods identified in guidelines. Non-health outcome relevant to the patient, or indirect impact on the quality of life of caregivers (e.g., family of the patient) will be considered on a case-by-case basis at the discretion of ACE's committees.	Included in supplementary analysis if important societal implications are involved (e.g., economic productivity impact).

ACE= Agency for Care Effectiveness; CBA= cost benefit analysis; CCA= cost consequence analysis; CUA= cost-utility analysis; FCA = friction cost approach; HAS = French National Authority for Health; HCA – human capital approach; HRQoL= Health related quality of life ; IQWiG = Institute for Quality and Efficiency in Health Care (Germany); MSAC= Medical and Scientific Advisory Council; NHS= National Health Service; NICE= National Institute for Health and Care Excellence; NIPH = Norwegian Institute of Public Health; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; QoL = quality of life; SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; UK= United Kingdom; ZIN= The National Health Care Institute;
a The document 'Handleiding intersectorale kosten en baten van (preventieve) interventies' published in 2014 by Maastricht University, is referenced for methods, however, the document is not in English and was not possible to retrieve from the source.
Source: ACE guidelines 2023; C2H guidelines 2022; CADTH guidelines 2017; CDE (TasPOR) guidelines 2006; HAS guidelines 2020; HIRA guidelines (Bae et al) 2022; HTAA guidelines (Lopez-Bastida et al) 2010; INESSS guidelines 2022 [36]; IQWiG guidelines 2022; KCE guidelines 2012; MSAC guidelines 2021; NICE guidelines 2022; NoMA guidelines 2018; PBAC guidelines 2016; PHARMAC guidelines 2022; SMC guidelines 2022; TLV guidelines for precision medicine 2022 [37]; ZIN guidelines 2016.

Three jurisdictions (the Netherlands (ZIN); Taiwan (CDE); Sweden (TLV)) states the societal perspective is used in economic evaluations for the reference case[1], For all other agencies (including for Australia), the healthcare payer perspective is considered for the reference case. As a result, except for the Netherlands (ZIN), it is recommended that inclusion of indirect and non-health benefits be presented as supplementary analyses to the reference case across all the jurisdictions/agencies.

Nine agencies recommended the inclusion of the impact of an intervention on caregivers QoL (England and Wales (NICE); Sweden (TLV); Scotland (SMC); Canada (CADTH); New Zealand, (PHARMAC); Singapore (ACE); Norway (NoMA); Belgium (KCE); Japan (C2H)). These agencies uniformly emphasise the inclusion of caregivers' QoL impact contexts particularly when the impact on family members is high or the intervention might have a measurable impact on the HR-QoL of others, such as family and caregivers, however, only the TLV in Sweden explicitly discusses the methods for how caregivers' QoL is to be included in economic evaluations. No additional information on how it is implemented is provided by the other agencies.

Only three jurisdictions (Canada (CADTH); the Netherlands (ZIN); South Korea (HIRA)) describe how inclusion of intersectoral costs and benefits should be factored into economic evaluations for HTA. PHARMAC state in their guidelines that costs to other non-healthcare government sectors arising due to pharmaceutical funding decisions should not be included; however, may be considered if they are significant. No details are provided as to what is considered significant.

While most agencies acknowledge the importance of non-health benefits and harms in supplementary analyses, few incorporate implications beyond direct health impacts into their reference case. This suggests that health outcomes remain the key factor in affecting reimbursement decisions for the majority of jurisdictions.

The Australian PBAC and MSAC guidelines are similar to those of the rest of the world in terms of considering these indirect and non-health benefits and harms; noting that Sweden is currently exploring methods and considerations for caregiver QoL with a particular focus on precision medicines. Although these outcomes are not considered in the reference case, the guidelines support presentation of these outcomes in supplementary analyses in evaluations or submissions.

1.3.3 Welfare impacts of listing a new medicine on the PBS

Under Australia's PBS system, there are two relevant prices that will determine the overall impact on societal welfare of listing a new medicine. The first is the price that is agreed between the sponsor of the medicine and the government, and the second is the price the consumer pays (or the copayment, which we will call the regulated price). In Australia there are three levels of copayment, in accordance with the safety net arrangements (the general copayment, the concessional copayment and a zero copayment after the safety net threshold has been reached).

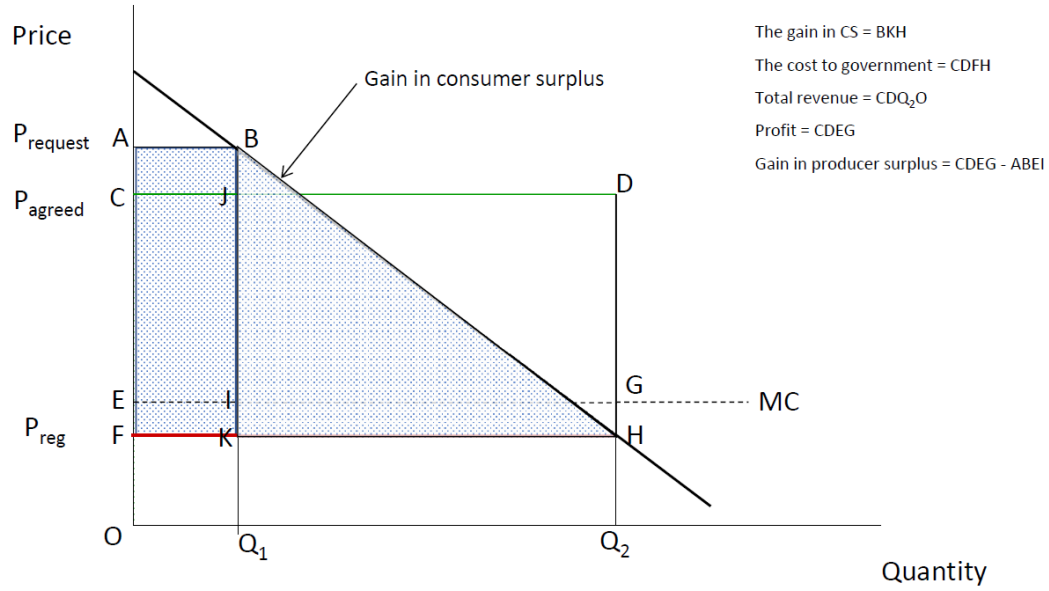
Before a medicine is listed on the PBS, if it has been approved for marketing by the TGA, there may be some demand for the medicine through the private market, but, for most new pharmaceuticals that offer a health improvement or other innovation (such as convenience in terms of mode of administration), the price in the private market tends to be prohibitively high which means that few consumers will be able to access the medicine through a private prescription. As a consequence, the revenue and therefore the profit to the sponsor, of private market sales, will be relatively small.

Once a medicine has been approved for listing on the PBS, the revenue will be determined by the agreed price, the demand at the regulated price and by any restrictions that are set by the PBAC recommendation.

This means that listing a medicine on the PBS leads to an increase in welfare to patients who are able to access the medicine at the copayment price (in economics terms this is the gain in consumer surplus). There is also an increase in revenue (and therefore profit) to the sponsor of the product. The revenue will be determined by the agreed price, and the quantity which is purchased/prescribed at the regulated price. This represents a welfare gain to the sponsor (in economic terms an increase in producer surplus).

These welfare gains to consumers and producers come at a cost to government, and ultimately to the Australian tax payers. The ultimate distribution of welfare impacts will be determined by the agreed price, but it is important to note that the welfare gains are shared between the consumers who are able to access the new medicine, and the sponsor, who makes a profit from the associated sales, with the costs being met by government (taxpayers). The distribution of welfare benefits from listing a new medicine is depicted in Figure 1.

Figure 1 Distribution of welfare impacts from a new drug listing



MC = marginal cost; $P_{request}$ = price requested by sponsor; P_{agreed} = price agreed between government and sponsor; P_{reg} = copayment.
Marginal cost in this example has been shown as constant and is indicative.

There is limited information in the market for new medicines to determine the appropriate agreed price. Health gains are often estimated in terms of gains in QALYs, but an actual market estimate of the value of an additional QALY is not possible, though the principle underlying the National Health Act is that the Australian government is willing to pay for additional health outcomes (QALYs).

For other benefits, such as convenience, one possible approach is to use stated preference methods to estimate consumer willingness to pay for this benefit. However, in eliciting such

values for convenience, the estimate represents the total value of the consumer surplus associated with being able to access the medicine with the associated benefit in terms of convenience. Therefore, it that estimate of value were to be used determine the agreed price between the government and the sponsor, in effect, all of the welfare benefits from listing the new medicine would be allocated to the sponsor (and all of the cost of these welfare benefits would be paid for by taxpayers), which would mean that there was no net welfare gain to the Australian population from this recommendation.

For example, suppose the estimated average WTP for the additional benefit across all consumers who access the new medicine is $x, and this is then used to set the price increase over the comparator to be $x. It is important to note that some consumers will have a higher WTP than $x and some will have a lower WTP than $x, but the government will pay $x additional for every script (noting that all consumers who have a WTP greater than the regulated price (the copayment) will likely access the new medicine). While there is still a welfare gain to those consumers, it is less than the additional cost to government (taxpayers) and so results in an overall welfare loss. In addition, it is important to note that consumers with a higher WTP may also have a higher ability to pay, and so using their stated WTP as part of the estimate may result in increased inequity. For this reason, while it is reasonable that the agreed price should reflect some of the welfare benefits to patients, if it captures all of these benefits, it transfers all of the consumer surplus to the sponsor with an associated cost to government (taxpayers), and may increase inequity.

1.3.4 Extrapolation and discounting in Australia and internationally+ (CHERE Discount rate review paper)

The need for extrapolation arises where clinical trial evidence, as may be used to construct a model based assessment of cost-effectiveness, does not reflect the anticipated time horizon over which costs and outcomes may accrue when the intervention is used in practice. Numerous agencies have recognised the significance of extrapolation of health benefits and costs in the context of economic evaluations. Several of these entities have offered explicit method recommendations, with the England and Wales (NICE) TSD 14 serving as a prominent reference for guiding the extrapolation procedure (Latimer 2011).

A comprehensive summary of the methods and processes used to extrapolate time -to-event data and discount health outcomes discussed in the guidelines of the jurisdictions of reference is presented in Table 8.

Table 8 Extrapolation methods recommended across agencies reviewed.

Jurisdiction (Agency)	Extrapolation		Discount rate
	Mentioned in Guidelines	Method suggested	
England and Wales (NICE)	Yes	Fit parametric survival models to the observed time-to-event data (i.e., exponential, Weibull, log-logistic, log-normal, gamma, Gompertz). More flexible extrapolation (e.g., piecewise spline models) if needed. Selection of the specific function for the base case analysis and the validation of the selected function.	3.5% for cost and benefits.
Australia (PBAC, MSAC)	Yes	As England and Wales (NICE)	5% for cost and benefits.
Scotland (SMC)	Yes	Not specified	3.5% for cost and benefits.
Canada (CADTH)	Yes	As England and Wales (NICE)	1.5% for cost and benefits.
New Zealand (PHARMAC)	Yes,	No methods specified	3.5% for cost and benefits.
France (HAS)	Yes	As England and Wales (NICE)	2.5% for cost and benefits the first 30 years. 1.5% for cost and benefits after 30 years.
Germany (IQWiG)	No	Not specified	3% for cost and benefits.
Norway (NoMA)	Yes	As England and Wales (NICE)	4% for cost and benefits the first 40 years, 3% from year 40 to 74 and 2% thereafter.
Sweden (TLV)	Yes	No method specified	3% for cost and benefits.
The Netherlands (ZIN)	Yes	As England and Wales (NICE)	4% for cost and 1.5% for benefits.
Belgium (RIZIV-INAMI)	No	Not specified	3% for cost and 1.5% for benefits.
Japan (C2H)	No	Not specified	2% for cost and benefits.
South Korea (NECA)	No	Not specified	5% for cost and benefits.
Singapore (ACE)	Yes.	As England and Wales (NICE)	3% for cost and benefits.
Taiwan (CDE)	No	Not specified	5% for cost and benefits.

ACE= Agency for Care Effectiveness; CADTH= Canadian Agency for Drugs and Technologies in Health; HAS= Haute Autorité de Santé; MSAC= Medical and Scientific Advisory Council; NA= not applicable; NECA = National Evidence-based healthcare Collaborating Agency (South Korea); NICE= National Institute for Health and Care Excellence; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; TSD= Technical support document; ZIN= The National Health Care Institute;
There was no information pertaining to extrapolation specified by these jurisdictions (Luxembourg; Spain;).
Source: ACE guidelines 2023, C2H guidelines 2022, CADTH guidelines 2017, CDE (TasPOR) guidelines 2006, HAS guidelines 2020, HIRA guidelines (Bae et al) 2022 , INAMI-RIZIV guidelines , IQWiG guidelines 2022, KCE guidelines 2012, MSAC guidelines 2021, NICE guidelines 2022, NoMA guidelines 2018, PBAC guidelines 2016, PHARMAC guidelines 2022, SMC guidelines 2022, TLV guidelines 2017 and ZIN guidelines 2016; Latimer TSD 14 [38].

All agencies recommend the time horizon used in a model, as necessitating the conduct of extrapolation, be long enough to capture all relevant benefits and costs of the intervention. Of those agencies, only the PBAC specifically states that caution should be taken so that the time

horizon of models (and hence the extent of extrapolation) is not unnecessarily extended, acknowledging the uncertainty that extended extrapolations bring to the decision-making process. Similarly, all agencies accept shorter time horizons, but only the guidelines for the PBAC/MSAC, England and Wales (NICE); SMC, Scotland; PHARMAC, New Zealand; NoMA, Norway; and TLV, Sweden specifically advise that a shorter time horizon may be appropriate for interventions not affecting mortality or with temporary health and QoL effects.

There are specific issues that arise pertaining to the extrapolation of data for vaccines as the benefits occur in the future. In Australia, Australian Technical Advisory Group on Immunisation (ATAGI) collaborates closely with PBAC to advise on vaccine assessment. Sponsors/manufacturers are required to seek advice from ATAGI on issues such as the applicability of effectiveness estimates in varying populations or settings, the validity of clinical predictions based on surrogate outcomes, and the extrapolation of effectiveness over time or throughout the community and/or select subpopulations within the community. ATAGI also provide specific advice on underlying assumptions regarding herd immunity, age-effects and any assumptions about key vaccine-related parameters that would be incorporated into cost-effectiveness modelling [39].

As demonstrated in the report prepared by CHERE and reviewed by the PBAC in 2022 reviewing the base discount rate internationally [40], there is considerable commonality across jurisdictions in terms of the discount rate applied to the discounting of costs and benefits. Among the 19 jurisdictions included in that analysis, current discount rates for costs and health benefits ranged from 1.5% to 5%, with 3% and 5% being the most common (5 of 19 (26%) each, respectively). Most of the jurisdictions listed have consistently applied equal discounting to costs and health benefits since 1990, with the exception of Belgium (which currently applies differential discounting), and France and the UK (both of which recommended differential discounting at some point in the past, but currently recommend equal discounting).

The majority of agencies reviewed were aligned with the PBAC/MSAC recommendation of applying a fixed discount rate over time. The report highlighted that there was minimal evidence provided in the literature or agency websites to provide a rationale for jurisdictions' choices of discount rate.

1.3.5 Assessment of economic uncertainty in Australia and internationally

There are numerous sources of economic uncertainty within HTA, which are generally described to fall in one of three broad categories: methodological uncertainty (the normative view about the 'best' approach for economic evaluations – including the choice of comparator, discount

rate and time horizon), structural uncertainty (the range of assumptions and judgements required in constructing an economic model) and parametric uncertainty (the uncertainty around the mean values of parameters used in the economic model).

All HTA guidelines address methodological uncertainty through the prescription of either a 'reference case' or 'base case', which specify the preferred methods in which to undertake economic evaluations. While there are some minor differences between jurisdictions in the extent to which submissions are required to conform to the prescribed reference- or base- case, all guidelines allow for deviations if they can be justified.

Additionally, all HTA guidelines recommend addressing structural and parametric uncertainty through undertaking some form of scenario or sensitivity analysis. While there is heterogeneity in preferred methods to address parametric uncertainty (deterministic vs probabilistic sensitivity analyses), most guidelines (including Australia (MSAC/PBAC)) provide the option to present both methods.

1.4 Part 2 - Special considerations for particular technology of populations types and sizes

1.4.1 Rare diseases and small patient populations

A universal definition of 'rare disease' has not yet emerged, and consequently, there is no corresponding universal definition for therapies for the treatment of rare diseases. The definitions used for orphan or rare diseases are often inconsistent from country to country [41]. The Australian DoHAC defines a disease as rare if it affects fewer than 50 in 100,000 people [42].

Eleven jurisdictions had some specifications in HTA guidelines or had programs applicable to health technologies for rare diseases (Australia (PBAC/LSDP); England and Wales (NICE); Scotland (SMC); Canada (CADTH); New Zealand (PHARMAC); France (HAS); Germany (IQWiG); Belgium (KCE); Singapore (ACE); South Korea (NECA); Taiwan (CDE, NIHTA, NIHA and HPA)). Three jurisdictions have specific pathways for ultra-orphan treatments (Australia; England and Wales; Scotland).

In Australia, medicines for ultra-rare and life-threatening diseases are predominantly paid for by the Commonwealth via the Life Saving Drugs Program (LSDP) or the PBS; but may be funded via joint Commonwealth and Jurisdictional funding arrangements under the National Health Reform Agreement. Drugs can only be submitted for LSDP consideration once they have undergone the PBAC review process and been deemed to be clinically effective, but not cost-

effective to list on the PBS. Once rejected by the PBAC on the basis of unacceptable cost-effectiveness, the sponsor may submit an application for listing on the LSDP. All applications seeking funding through the LSDP are considered by the LSDP Expert Panel [43]. For consideration for the LSDP the treatment must also meet the LSDP criteria.

In England and Wales, the Highly Specialised Technology Program considers drugs for ultra-rare conditions with topics identified by the National Institute for Health Research Innovation Observatory. Within the Highly Specialised Technologies Program a higher threshold for cost-effectiveness of the technology is applied (£100,000 QALY gained). The size of benefit is also considered where a weight is applied for HSTs.

In Scotland (SMC) medicines meeting specific criteria can be processed under the 'ultra-orphan pathway' [44]. Through this pathway, medicines can be made available in Scotland for a period of three years (during the evidence generation stage) prior to a decision being made (during reassessment) on routine use in NHS Scotland. If the SMC advice is 'not recommended' the sponsor can request to convene a Patient and Clinician Engagement (PACE) meeting. This is an additional meeting of patient groups and clinicians to explore the value of the medicine, that may not be fully captured within the conventional clinical and economic assessments [45].

In Germany (IQWiG and G-BA), an added benefit is assumed to be proven for orphan drugs at the time of EMA approval for subsequent market access. The HTA process for orphan drugs does not require an economic evaluation if the annual turnover is less than €50 million.

Separate evaluation committees have been established in some jurisdictions, including Australia, to evaluate technologies for rare disease. For all jurisdictions with established rare disease committees, consideration of patient input is factored into their decision-making framework. Evaluations for drugs for rare disease are generally based on clinical and economic evidence, but most HTA agencies/organisations do recognise the impact of the paucity of robust clinical and economic evidence when assessing drugs for rare diseases.

1.4.2 High unmet clinical need and equity considerations

Unmet clinical need is often incorporated informally in decision-making processes, with evidence of significant influence on approvals for orphan drugs [46]. The MSAC guidelines recommend that the affected subgroups should be identified for health technologies that address health inequalities (e.g., those resulting from differences in access to care in rural and remote areas, or an area of unmet clinical need). The PBAC guidelines describe 'clinical need' as one of the less-readily quantifiable factors influencing PBAC decision making. Decisions made by the PBAC in areas of unmet clinical need can be recorded in public summary documents. Unmet

clinical need was not explicitly addressed in any of the other international HTA guidelines reviewed.

A limited number of HTA guidelines explicitly mention that equity implications of the technology are important and should be considered (Australia (MSAC/PBAC); Canada (CADTH); England and Wales (NICE); Korea (HIRA); Scotland (SMC); Spain (HTAA); Taiwan (CDE)). In each case, consideration of equity occurs alongside cost-effectiveness analyses with all guidelines recommending equal weighting of QALYs for the base case analysis, regardless of the characteristics of people receiving, or affected by, the intervention in question. Three agencies (England and Wales (NICE); the Netherlands (ZIN); Norway (NoMA/NIPH)) have operationalised the practice of applying equity weights to specific population subgroups as a means of increasing the effective cost-effectiveness threshold for some new health technologies. In other jurisdictions, qualitative deliberation is the method in which factors for equity are considered.

In light of higher burdens of disease and challenges in accessing health care services among Aboriginal & Torres Strait Islander and Maori populations respectively, Australia and New Zealand have adopted special authority ethnicity criteria for some medications [47] [48]. New Zealand has also piloted an equity capability self-assessment tool with the PTAC [48].

Methods to quantify the equity impacts of health technologies, namely distributional cost-effectiveness analysis (DCEA) [49], have been explored in the literature but are yet to be implemented in practice. The feasibility of incorporating DCEA within HTA processes is currently being explored in England and Wales (NICE) [50], however challenges arising from a lack of consistency in how equity concerns are defined and how data are collected or reported have been described [51].

1.4.3 Co-dependent technologies

Technologies are co-dependent when their combined use (sequentially or simultaneously) achieves or enhances the intended clinical effect of the technologies separately. The Methods Review found that the methods employed with respect to co-dependent technologies do not differ significantly from those used for assessing single technologies. Key considerations such as effectiveness, cost-effectiveness, and safety remain crucial in the assessment of co-dependents. However, there are distinctions in the evaluation process and evidence requirements for co-dependents as compared with single technologies.

Information on the processes and evidence accepted for co-dependent technologies were explicitly noted in the HTA guidelines of eight jurisdictions: Australia (PBAC, MSAC); England and Wales (NICE); Scotland (SMC); Canada (CADTH); France (HAS); Sweden (TLV); Belgium (RIZIV-

INAMI); Singapore (ACE). Six jurisdictions have joint processes in place for the evaluation of co-dependent technologies (Australia, PBAC and MSAC; England and Wales, NICE; Canada; France, HAS; Belgium, RIZIV-INAMI; Singapore, ACE). Sweden's (TLV) guidelines do reference the use of companion diagnostics in relation to precisions medicines and advanced therapy medicinal products (ATMPs) however the HTA process undertaken in Sweden is unclear. The SMC in Scotland noted that the process for the review of diagnostics is referred to the Scottish Genomic Test Advisory Group (SG-TAG) or Scottish Pathology Network (SPaN), as appropriate, who advise SMC on the diagnostic testing aspects of the economic case. Belgium (RIZIV-INAMI) implemented a joint process in 2019, where it was considered that a desynchronised decision-making process hindered access for these technologies.

In Australia, an integrated (MSAC and PBAC) co-dependent application is required if the co-dependent technologies include a medical service or diagnostic test not currently publicly reimbursed ([52]). A streamlined co-dependent submissions or separate submissions for each technology (one for the test and one for the medicine) is applicable when one committee has indicated support for the technology pairing after previous consideration, or if a minor amendment is needed for an MBS item descriptor to enable access to a co-dependent medicine in the same therapeutic class as a previously PBS-listed medicine. Integrated MSAC and PBAC co-dependent applications are considered in parallel or jointly by the PBAC and the MSAC, which often results in longer times for the decisions being made [53].

1.4.4 New and emerging technologies

Many new complex therapies have emerged with a prominent focus on personalised health technologies, which may combine a growing number of technologies, including pharmaceuticals, devices, diagnostics, and digital tools. These new and emerging technologies represent medical advancements in personalised treatments and treatment pathways e.g., gene therapies, cell-based therapies, precision medicines, personalised medicine approaches, advanced biologics, and innovative medical devices. Two agencies (England and Wales, NICE; Sweden, TLV) are attempting to address the area of new and emerging technologies. In 2021, the TLV in Sweden, issued guidance on this topic (titled "Health-economic assessments and payment models for precision medicines") [54]. In July 2019, the NICE began a review of its evaluation methods, resulting in a report entitled "CHTE methods review. Developing the manual. Task and finish group report" published in August 2021 [55].

The TLV in Sweden concluded that the main obstacle to identifying the value of precision medicine and ATMPs is the lack of evidence for how large the health benefits will be from various treatments and tests – compared to the alternative and in the long term.

NICE in the UK presents an interesting case of the need for updating the evaluation guidelines to include new methods for new and emerging technologies. In 2017, a report commissioned by NICE determined that its standard HTA methods and processes for evaluating clinical and cost-effectiveness were generally appropriate for ATMPs [56] [57]. Recognising the uncertainty and potential patient benefits inherent in such technologies, NICE conceded the need for inventive payment mechanisms to manage risk. This realisation led to the 2021 review of methods for complex technologies, albeit with limited integration of proposed methods addressing new and emerging technologies associated with limited knowledge of long-term outcomes [58].

The Methods Review of international guidelines showed differing approaches toward integrating new evaluation methods for emerging technologies. Notably, the methodologies proposed by Sweden (TLV) and the proposal of new methods by the NICE, review contrast with the guidelines of PBAC and MSAC that do not outline methods that address the challenges of new and emerging technologies. Subject to the emerging experience from the use of those guidelines, it may be appropriate to adapt the existing Australian guidelines to incorporate methods specific to the evaluation of specialised technologies.

1.4.5 Multiple small populations/sub-groups, and flow-on effects for pricing

HTA processes are conducted for a single-indication at a time, which is a consistent process internationally. Manufacturers/sponsor launch products for single-indications where the initial indication is for a high severity disease or the indication fulfils an unmet need. However, health technologies are being developed for multiple indications, which have varying degrees of clinical benefit across these patient populations. The value of first indication compared with subsequent indications can be a major challenge where price is based on the initial indication. Three methods for flow-on pricing for multi-indication products are described in the literature [59, 60]: 1) single price policy, where the same price is applied irrespective of indication (there is no consideration of indication specific prices, weighted or otherwise); 2) indication-based pricing, where a differential price is applied according to benefit or value delivered for each indication; and 3) indirect indication-based pricing methods, which is described as differential discount, weighted-average prices, clinical restrictions, and use of financial and outcome based managed entry agreements.

In Australia, as HTA is conducted by a single-indication at a time; indirect indication-based pricing methods are applied using SPAs, RSAs, or other types of agreements. Indirect indication-based pricing methods is the most common approach identified across jurisdictions [59, 60].

1.5 Part 3: Recent reforms to economic evaluation processes and methodology in Australia and internationally

Ten agencies have updated their methods and process guidelines since 2020 (Australia, MSAC in 2021; England and Wales, NICE in 2022; Scotland, SMC 2020-2022; New Zealand, PHARMAC in 2020; France, HAS in 2020; Germany, IQWiG in 2022; Norway, NIPH in 2021; Singapore, ACE in 2021 to 2023; South Korea, HIRA in 2021; Japan, C2H in 2022). Many of these changes with respect to HTA methodology and considerations have been discussed in Part 1 and Part 2 of this report. The guidance from these agencies covers health technologies including medicines and vaccines, as well as co-dependent technologies. However, these guidelines provide little or no reference to highly specialised therapies, such as cell and gene therapies.

Only the TLV in Sweden has published guidance (in 2021 and 2022) with respect to methods for identifying the value of precision medicines and ATMPs. NICE are also currently planning to develop targeted processes and methods for cell and gene therapies, artificial intelligence and genomics. However, guidance for HTA methods for these technologies has not yet been issued.

There have been many reform initiatives relating to the regulatory processes and HTA pathways for reimbursement for the PBS and the MBS since 2009. The Managed Entry Scheme (MES) as a formal process in 2010. The aim of the MES was improving patient access by reimbursing drugs on the condition that further evidence is provided. Uptake of MES in Australia has been low [61]. Managed agreements based on outcomes have been challenging in practice [62]. The TGA and PBAC Parallel Process was introduced for medicines in 2011 and in 2017 for vaccines. This arrangement enables sponsors to submit medicines for concurrent evaluation by the TGA and the PBAC to expedite listing and subsidy of new innovative medicines in Australia. This process has led to faster access of new and innovative medicines.

PBS Process Improvements have been implemented in a two staged approach (based on Clause 10, Strategic Agreement 2017) [63]. Stage 1 PBS Process improvements commenced on the 1st of July 2019 including: 1) Changes to pre-submission meetings to provide additional guidance and support for complex submissions; 2) Introduction of a compulsory intent to apply step for Major and Minor submissions; and 3) Introduction of four new transparent pathways following a positive PBAC recommendation. Stage 2 PBS process Improvements commenced 1st of

January 2021 including: 1) Changes to initial submission categories (including introduction of a single submission date); 2) Introduction of resubmission pathways for submissions not recommended by the PBAC; 3) Revised cost recovery arrangements to support implementation of Stage 2 process improvements; and 4) Other improvements, including expansion of the department's Health Products Portal functionality. One of the process improvements was to develop key metrics, for which data are collected and published for the time taken to list a medicine on the PBS [64]. In 2021, DoHAC commenced work to support reforms and improvements to the Prostheses List; where new arrangements from this work has only recently been implemented (1st of July 2023) [65].

The SMC introduced a fast-track resubmission process from January 2020 for submissions where the only change is a new or improved simple Patient Access Scheme (PAS) or if the point of the resubmission is a change to the confirmed price list.

In July 2019, NICE initiated major reforms of their health technology evaluation methods guide, which outlined a 5-year strategic plan providing the framework for the direction and priorities for NICE. In 2022, NICE developed a 'Proportionate approach' to technology appraisals with the aim of increasing capacity to be able to produce more guidance, thereby reducing the time in conducting appraisals, and to enable decisions to be made faster [66]. Two different methods/streamlined approaches currently being piloted using the proportionate approach include the: Cost comparison approach (formerly known as 'fast track approvals'); and Streamlined decision-making for technology appraisals that are beyond those suitable for cost comparison but are considered to be lower risk for patients, the NHS, stakeholders and NICE.

NICE are also exploring whether particular assumptions could be pre-specified at the start of an evaluation, and the use of using a pre-built economic model to be used for ongoing evaluations, which is an approach that departs significantly from the current single technology appraisal. This approach requires long-term development and is currently being piloted over 2023-24 for technologies used in renal cell carcinoma and non-small cell lung cancer.

2. Background

As part of the Strategic Agreement with Medicines Australia (2022–2027), the Australian Government has commissioned an independent review of current health technology assessment (HTA) policies and methods used by the Pharmaceutical Benefits Advisory Committee (PBAC) to assess new medicines for listing on the Pharmaceutical Benefits Scheme (PBS), contemporary research, and relevant methodologies and purchasing practices used by comparable international jurisdictions.

HTA is a multidisciplinary framework used to inform decision-making processes for the adoption of health technologies, and increasingly, is being institutionalised into national health policies. In Australia, HTA is used to support decisions related to the listing of medicines and vaccines on the PBS and medical services/technologies on the Medicare Benefits Schedule (MBS).

HTA in Australia

Australia has had a long history of using HTA for the consideration of reimbursement of health technologies. In 1992, Australia was one of the first countries to require evidence to be submitted to decision-makers for the reimbursement of pharmaceuticals, and over time many other jurisdictions have developed their HTA practices. The comparisons of HTA processes and methods in Australia with other jurisdictions are discussed in the main body of the report. This section briefly summarises HTA processes in Australia.

There are two main health technology advisory committees that use HTA to assess whether health technologies qualify for subsidisation by the Australian Government. The PBAC appraises medicines for public funding via the PBS and the Medical Services Advisory Committee (MSAC) considers medical services for public funding on the MBS. In Australia, the current PBAC process is submission driven, as the process is highly dependent on sponsor companies (those responsible for the supply of the relevant medicines) seeking PBS listing.

The HTA process for pharmaceuticals and vaccines requires an externally prepared application, which is reviewed by the Department of Health and Aged Care (DoHAC), and independent external consultants (i.e., evaluation groups – typically located within universities across Australia). The PBAC is supported by three committees, the Economic Sub-Committee (ESC), the Drug-Utilisation Sub-Committee (DUSC) and the Nutritional Products Working Party (NPWP).

- ESC: reviews and interprets economic analyses submitted by the applicant, and the accompanying Commentary prepared by external evaluators, seeking to list a medicine

on the PBS. The ESC advises the PBAC on the quality, validity and relevance of these submissions, and is also responsible for advising the PBAC on methodological developments on the collection, analysis and interpretation of clinical and economic data. ESC considers all Category 1 and Category 2, and standard re-submissions to the PBAC.

- DUSC: examines the utilisation of PBS items when there is at least 24 months of prescription data available and where DUSC or the PBAC has highlighted items of interest. Utilisation analyses are publicly available [67] [68]. DUSC considers all Category 1 submissions and a selection of Category 2 submissions to the PBAC. DUSC advises the PBAC and the applicant on important matters relating to the use and cost estimates within submissions to list medicines on the PBS, and reviews utilisation of currently listed PBS medicines.
- NPWP: provides advice to the PBAC on clinical and financial matters for nutritional products (medicinal foods e.g., special infant oral formula and food substitutes to treat inborn errors of metabolism) as well as any matters relating to utilisation of PBS-listed nutritional products referred to them by the PBAC.

The PBAC also provides recommendations for vaccines requesting listing on the National Immunisation Program (NIP) and the PBS. Applicants must seek advice from the Australian Technical Advisory Group on Immunisation (ATAGI) prior to making a PBAC submission. The ATAGI/PBAC HTA process is described in published guidance documents [69, 70].

The process undertaken by the Australian Government DoHAC for the listing of medicines and vaccines is outlined in the 'Procedure guidance for listing medicines on the PBS and on the NIP' [21]. The Procedure guidance and forms have recently been revised [21, 71]. There are six types of submissions used for listing medicines on the PBAC and vaccines on National Immunisation Program (NIP) [21]:

- Category 1: submissions requesting a listing for PBS or NIP that is: 1) first in class, and/or medicine/vaccine for a new population; 2) a co-dependent technology requiring an integrated application for MSAC and PBAC; 3) a drug/vaccine with a Therapeutic Goods Administration (TGA) provisional determination. Category 1 submissions require the PBAC to assess the magnitude of clinical improvement or toxicity reduction, the incremental cost and the comparative costs and outcomes where an economic evaluation is required to support a claim of cost-effectiveness, cost-utility or cost-minimisation.

- 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. They may also relate to a request for the PBAC to reconsider an existing recommendation where there is a change to the clinical, economic and/or financial information most recently relied on by the PBAC. A Category 2 submission may be required for a new form or strength of an already-listed medicine or vaccine that is not bioequivalent to an existing listed form of the medicine or vaccine. This may be necessary to demonstrate that the new form delivers similar clinical outcomes to the existing form.
- Category 3: generally, relates to requests to change existing listings that do not change the population or cost-effectiveness of the medicine or vaccine that do not meet the criteria for a Category 4 submission. This includes requests to enter into a deed or vary an existing deed of agreement. Although, the PBAC assess the clinical need for and clinical effectiveness of the requested listing, an economic evaluation is not necessary. Additionally, Category 3 submissions do not require the PBAC to assess any substantial financial implications for the supply of a listed medicine or designated vaccine. PBAC advice may also be required through a Category 3 submission process in some other circumstances (e.g., requests for PBS listing of nutritional products (medicinal foods) or some new brands of existing pharmaceutical items with an unusual presentation; or advice on potential equivalence, substitution, or issues related to quality use of medicines).
- Category 4: involve a request for one of more of the following: 1) Listing of a new pharmaceutical item of a listed medicine; 2) Consideration as an exempt item (Exempt item as per subsection 84AH of the National Health Act 1953); 3) Including a listed medicine on the prescriber bag, or varying an existing prescriber bag listing; 4) A change to the existing, or the addition of a new form or manner of administration of a listed medicine; 5) A change to the maximum quantity and/or number of repeats of a listed medicine; and 6) A change or addition to the prescriber type(s) of a listed medicine.
- Committee secretariat submissions: relate to applications where the requested listing changes do not require the PBAC to consider comparative effectiveness, cost-effectiveness or clinical need.

- Application for a new brand, or new oral form, or an existing pharmaceutical item: Applications that do not require PBAC consideration for listing an additional brand (i.e., generic medicine) or new oral form of an existing TGA-approved and PBS-listed pharmaceutical item should be lodged directly to the department. Evidence of equivalence from the TGA must also be provided.

Applicants who choose to request reconsideration of a Recommendation are required to advise the Department and follow the processes for lodging a submission [21].

There are four different resubmission pathways available to applicants following a 'not recommended' PBAC outcome. Resubmission pathways are not available for submissions that receive a positive recommendation from the PBAC. The PBAC nominate a resubmission pathway based on their assessment of 1) issues for resolution; and 2) whether the medicine or vaccines represented High Added Therapeutic Value (HATV), which addresses two criteria: i) a high and urgent unmet clinical need; and ii) expected to provide a substantially and clinically relevant improvement in efficacy or reduction in toxicity over any alternative therapy. The four resubmission pathways are as follows [21]:

- Standard Re-entry pathway: Applications with a PBAC outcome of 'not recommended' are able to lodge a resubmission through the standard re-entry pathway. This is the default pathway for resubmissions.
- Early Re-entry pathway: where the PBAC considers that the remaining issues could be easily resolved, and the medicine or vaccine does not represent HATV for the proposed population. This includes circumstances where: 1) new clinical study data requiring evaluation is not considered necessary to support new clinical claims made in the resubmission; and 2) a revised model structure or input variable changes are not necessary to support a new economic claim, or to estimate utilisation or financial impacts. Applicants accepting this pathway are eligible for PBAC consideration at the next main PBAC meeting.
- Early Resolutions Pathway: where the PBAC considered the remaining issues could be easily resolved (as per Early Re-Entry Pathway) and where the medicine or vaccine meets the HATV criteria. Applicants who accept this pathway are eligible for PBAC consideration out-of-session (before the main meeting), unless the Department, in consultation with the PBAC Chair, identifies an unexpected issue such that the resubmission needs consideration at the next main PBAC meeting (in March, July or November).

- Facilitated Resolution Pathway: where the PBAC considers the issues for resolution could be explored through a workshop and where the medicine or vaccine meets the HATV criteria. Applicants who accept this pathway are eligible for a solution-focussed workshop with one or more members of the PBAC [21]. It is expected that Facilitated Resolution Pathway resubmissions will require evaluation of a new and/or updated model structure and/or input variable changes beyond those specified by the PBAC to support the economic claims or estimate the utilisation and financial impact in the resubmission. This may also include other substantial changes from the previous submission that require re-evaluation.

The Standard Re-Entry Pathway applies to applicants who choose not to accept pathways nominated by the PBAC or if they are unable to meet the lodgement timeframes. Evaluation of applications to the PBAC is conducted over a 17-week cycle; this includes assessment of the evidence by the external evaluators, meetings of the ESC and DUSC, sponsor feedback on those assessments and the PBAC meeting.

Finalisation of pricing and budget impact is conducted with the applicant and Department of Finance and other government agencies after the PBAC has recommended the medicine for listing [21]. There are five pricing pathways (which do not apply to generic medicines or the post-PBAC processes for vaccines).

- Pricing Pathway A – Facilitated: The PBAC determine eligibility for Pricing Pathway A as part of its recommendation. This pathway applies for submissions, where the PBAC considers: 1) the medicine is expected to provide substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over any alternative therapies; 2) the medicine addresses a high and urgent unmet clinical need; and 3) it would be in the public interest for the submission to be recommended to follow this pathway.
  The applicant either accepts the PBAC's recommendation for Pricing Pathway A or nominates another pricing pathway.
- Pricing Pathway B – New deed: Applies to submissions which require negotiation and finalisation of a new deed of agreement where there are no similar arrangements in place. This could include an assessment of proposed risk-sharing, managed entry and/or special pricing arrangements.
- Pricing Pathway C – Existing deed: applies to submissions which require third-party responsible person notification of changes to an existing deed of agreement, and/or where an applicant has received a positive PBAC recommendation to list within the

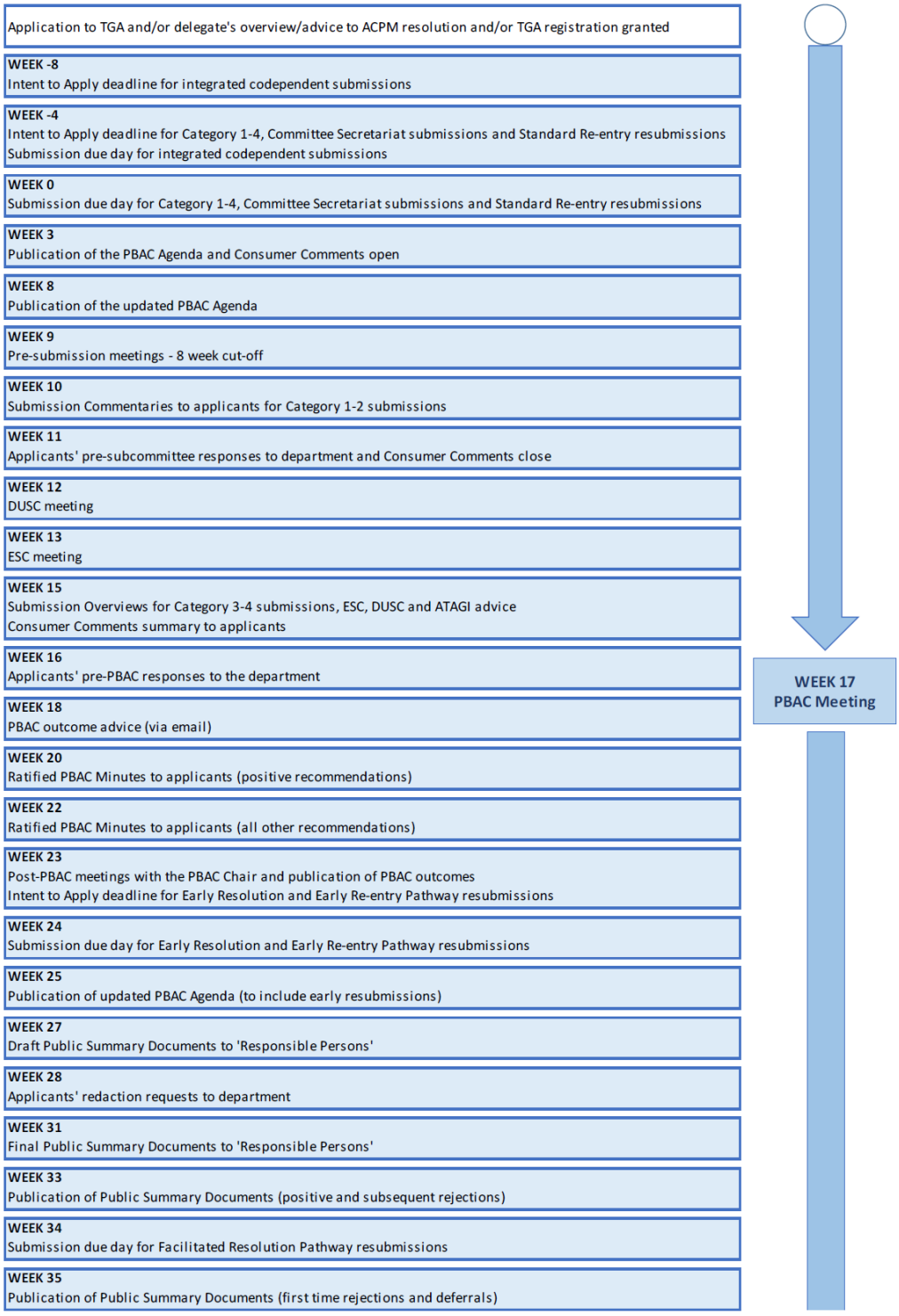
scope of existing arrangements, whether these relate to the new listing or to another existing listing.

- Pricing Pathway D – No deed: applies to submission which do not involve negotiation of a new or existing deed of agreement.
- Secretariat Pricing: applies to changes to listing of existing medicines which do not require a new price.

The PBAC makes recommendations based on factors including but not limited to: comparative health gain; comparative cost-effectiveness; patient affordability in the absence of PBS subsidy; predicted use in practice and financial implications for the PBS and the Australian Government health budget; overall confidence in the evidence and assumptions relied on in the submission; equity; presence of effective therapeutic alternatives; severity of the medical condition treated, ability to target therapy with the proposed medicine; and issues affecting public health [72]. The PBAC aim for consistency and fairness in decision-making across all medicines and clinical areas, however, different levels of evidence and certainty, and cost-effectiveness are considered in relation to clinical need, and rarity of medical conditions [73].

The process for submissions and resubmissions to the PBAC is presented in Figure 2.

Figure 2 Timeline of PBAC procedures



ACPM = Advisory Committee on Prescription Medicines; ATAGI = Australian Technical Advisory Group on Immunisation; DUSC = Drug-Utilisation Sub-Committee; ESC = Economics Sub-Committee; PBAC = Pharmaceutical Benefits Advisory Committee; TGA = Therapeutic Goods Administration.
Source: Figure 2.1, Procedure guidance for listing medicines on the PBS [21].

Applications for the funding of medical, diagnostic and imaging services are considered by the MSAC and relates to new services funded under the MBS, co-dependent technologies, as well as applications for funding outside the MBS such as for the National Product Price List for blood products, Highly Specialised Therapies under the National Health Reform Agreement (NHRA),

and government funded screening programs. Applications for MSAC can be made by industry, those in the medical profession or other stakeholder groups [74]. The MSAC is supported by two committees; PICO Advisory Sub-Committee (PASC) and the Evaluation Sub-Committee. New applications are processed under three pathways with the timeline varying depending on which pathway is adopted [75]:

- Standard: primary pathway for the majority of applications. The pathway requires development of a PICO by an HTA group, is considered at one PASC meeting, and development of an assessment report by either the applicant or contracted by the DoHAC that is to be considered by the Evaluation Sub-Committee and MSAC.
- Comprehensive: follows the process as the Standard pathway, but requires one additional consideration by PASC and a formal consultation period between the two PASC meetings.
- Expedited: used where the PICO is clear in the application form, and the DoHAC and MSAC executive agree the application can bypass PASC and progress to the development of an Assessment Report to be considered by Evaluation Sub-Committee.

The MSAC provides advice on MBS fees; however, the MBS fees are not set by MSAC [76].

Whilst the assessment of pharmaceutical technologies via the PBAC is embedded in the legislation, the assessment of medical technologies/services for inclusion on the MBS is non-statutory [73]. This is an important distinction affecting the operation of the two committees (PBAC and MSAC) and the avenues by which changes in their processes may be enacted (i.e., changes to the PBAC process may require legislative amendment). For example, under the National Health Act (1953), the Minister of Health makes decisions about the listing of medicines on the PBS subject to the advice of the PBAC as a legislative committee (the Minister cannot list a medicine on the PBS without a prior recommendation to do so from the PBAC). In contrast, MSAC is a non-legislative committee, and so its advice is not binding - the Minister for Health will decide whether MBS funding will be granted.

3. Purpose and structure of the paper

The purpose of this paper is to discuss Australian and international approaches to economic evaluation, special considerations for technologies, and recent reforms in economic evaluation processes. The paper provides an overview of the methodologies used in economic evaluation to support HTA processes in Australia and other jurisdictions of interest where HTA is used to support reimbursement for new health technologies.

Paper 5 – HTA Methods: Economic evaluation

Based on guidance provided by the Reference Committee of this Review, the jurisdictions included were the United Kingdom (UK) (England and Wales; Scotland), Canada, New Zealand, France, Germany, Norway, Spain, Sweden, The Netherlands, Belgium, Luxembourg, Japan, South Korea, Singapore, and Taiwan. Although, methods from other jurisdictions were considered if relevant to the Australian Health System.

Australia, the UK, and Canada are often cited as jurisdictions in which the HTA systems are well established within the health policy framework. Other early adopters of HTA include New Zealand, France, Germany, Sweden, the Netherlands. More recent adopters of HTA processes include: Japan, South Korea, Singapore, Taiwan; and Norway, Spain, Belgium and Luxembourg. Across these jurisdictions, HTA systems vary in how they are organised, and in the evidentiary requirements used for the assessment of health technologies, which can influence the ways in which HTA functions [77].

This paper will describe the methods used in economic evaluation (Part 1), special considerations for particular technologies and for specific populations (Part 2), recent reforms and changes to economic evaluation processes and methods (Part 3). A comparative framework of economic evaluation methods used across jurisdictions is included so that the similarities, differences and relevance to the Australian setting can be evaluated.

The topics covered in this paper include:

Part 1: Economic evaluation methodology

- Approaches to economic evaluation in Australia and internationally
- Weighting of health outcomes and risks/harms: Weighted scales, patient relevant outcomes, patient preferences, indirect and non-health benefits/harms
- Extrapolation and discount rates
- Assessment of economic uncertainty in Australia and internationally

Part 2: Special consideration for particular technologies

- Rare diseases and small patient populations
- High unmet clinical need and equity considerations
- Co-dependent technologies
- New emerging technologies
- Multiple small populations and flow on effects for pricing

Part 3: Recent reforms

- Processes and the alignment with health technologies
- Outcomes of reforms

4. Methods

Information pertaining to economic evaluation methods were garnered from several sources, including websites of national HTA agencies, organisations and societies, the published literature, and through interviews with key stakeholders from within these jurisdictions. Findings are presented by topic heading.

4.1 Website searches

A search of the websites of the national/jurisdictional HTA agencies and the coordinating Department/Ministry of Health for each of the countries/jurisdictions was conducted to identify documents providing economic evaluation guidance to sponsors/suppliers of health technologies over May to July 2023. Documents issued by the HTA agencies were examined specifically to identify recommendations outlining the recommended, preferred or required methods to be used for economic evaluation. Documentation providing economic evaluation guidance to sponsors and suppliers of health technologies, including HTA guidelines, HTA processes, technical reports, policy documents, position statements, or memos relating to economic evaluation methods were included for review. The extent to which these methods are formalised, for example, preferred, recommended or not stated in the guidelines and other related documentation was examined. The websites of HTA organisations and societies and consumer representative organisations were also reviewed to further understand the processes, advice and recommendations given to applicants (see Table 27 and Table 28 in Appendix 1).

4.2 Targeted literature searches and grey literature

To supplement information retrieved from the websites of the national HTA agencies and the coordinating Department/Ministry of Health, a targeted literature review was undertaken in PubMed and EMBASE. The HTA review conducted by the Australian Department of Health in 2009 was considered highly relevant, and used as an initial point of reference in identifying the available literature. Papers that discuss HTA methods and processes used by HTA agencies to consider reimbursement, including systematic reviews, reviews of cross-country comparisons were tabled and assessed for relevance. Searches were limited to papers published in English from January 2013 to June 2023. Relevant references were identified through snowballing where reference lists of included papers, which discussed the benefits, risks and limitations of

the HTA processes and economic evaluation methods outlined by the national HTA agencies are presented throughout the paper.

4.3 Stakeholder interviews

Although HTA guidelines and websites are typically clear and detailed (from the agencies of some/most countries/jurisdictions), some aspects of HTA policy and practice may not be sufficiently detailed in publicly available documentation, and therefore stakeholder interviews were conducted to consult Government authorities, HTA agencies, industry peak bodies and consumer representative organisations, in Australia and internationally about their country specific HTA processes. Direct consultation was conducted using semi-structured interviews. Interviews were undertaken virtually (i.e., online) using a secure video conferencing platform (i.e., Zoom; WebEx). With participant consent, interviews were audio-recorded and transcribed for subsequent analysis. All interview data were de-identified (i.e., interviewees were referred to only with respect to their national and professional setting, e.g., 'HTA expert; HTA agency representative'). The interview protocol is provided in Appendix 2. A summary of the jurisdictions included in the stakeholder interviews is provided in Table 1.

Ethical approval for this study was obtained from the University of Technology Sydney (UTS), Human Research Ethics Committee (HREC) (UTS HREC Reference number: ETH23-8318). Four group consultations were conducted with stakeholders in Australia including:

- Members from PBAC and ESC, DoHAC (Office of Health Technology Assessment, National Blood Authority (NBA), Life Saving Drugs Program (LSDP), PASC, MSAC Secretariat, HTA Review Secretariat).
- Industry via a meeting auspiced by Medicines Australia.
- Post PBAC processes with officials from the DoHAC with responsibility for the PBS Pricing and Managed Access Section.
- Individuals from External Evaluation Groups (to the PBAC).

Table 9 Stakeholder consultations - international

Jurisdiction	Stakeholder group (N=12)
England and Wales	Expert x 2
Scotland	Agency
Germany	Expert x 1; Agency x 1
Spain	Agency x 2
Taiwan	Agency
Thailand	Agency
Singapore	Agency
South Korea	Expert

Jurisdiction	Stakeholder group (N=12)
United States of America	Agency

Representatives were also approached from Canada, New Zealand, France and Japan. Representatives from Japan would only participate if they received payment; this was outside of the ethics approval for interview conduct and further contact with those representatives was not pursued. Representatives from the other jurisdictions did not respond to requests for interview.

5. Findings Part 1: Methods in economic evaluation

The aim of this section was to outline the acceptable and preferred methodologies used by HTA agencies. This may inform work-sharing practices later. Shared practices may focus on technical evaluation rather than appraisal and decision-making.

Approaches to economic evaluation in Australia and internationally

HTA systems globally

There are differences in the way HTA systems are set up across countries. These differences reflect differences in health system priorities, culture, values and preferences. Variations in the organisation of HTA systems are also due to factors such as governance, roles, remit, and scope [77]. HTA processes may be coordinated by different organisations or departments within a country or jurisdiction. For example, economic evaluation may be conducted by organisations separate from organisations/departments responsible for pricing, and these processes may be conducted at different times prior to consideration of reimbursement.

The extent to which HTA processes rely on the results from economic evaluations for decision-making and reimbursement also differs across jurisdictions. Of the jurisdictions reviewed, twelve formally use economic evaluation in decision-making (Australia; England and Wales; Scotland; New Zealand; Canada; The Netherlands; Belgium; Norway; Sweden; Singapore; South Korea; Taiwan). Japan only formally uses economic evaluation as part of drug price reviews in cases where price premiums are considered [78]. In France, HTA processes are primarily used for price setting and not reimbursement, where Haute Autorité de Santé (HAS; French National Authority for Health) determine the Amelioration du Service Medical Rendu (ASMR; French High Authority of Heath Scale) rating and then specify cases where economic evaluation will be required for drugs and devices; the Economic Committee for Health Products (CEPS) then determines price, which is covered by national health insurance [79]. Two jurisdictions, Germany and Spain, do not use economic evaluations for decision-making.

Perspectives

Three jurisdictions (the Netherlands (ZIN); Taiwan (CDE); Sweden (TLV)) states the societal perspective is used in economic evaluation for the reference case[2] [13]; for all other agencies,

[2] A reference case gives a formal statement of accepted methods and assumptions underpinning analyses to which submissions should conform.

the healthcare payer perspective is considered for the reference case. This differentiation in perspective results in different methods being considered by the Netherlands, particularly relating to inclusion of costs and benefits in modelling.

Systematic review of economic evaluations

Eight agency guidelines request that sponsor applications include a systematic review of previous economic evaluations (Australia, PBAC and MSAC; England and Wales, NICE; Scotland, SMC; Canada, CADTH; Japan, C2H; Taiwan, NIHTA; France, HAS). Guidelines from other jurisdictions state that they consider it useful to perform such a review (Belgium, KCE; the Netherlands).

Selection of comparators

HTA is essentially a comparative assessment. In order to make an assessment of the impact of a health technology on the health of patients, the new technology must be compared to existing technologies. The claims for a new technology will therefore depend on the comparator(s) nominated and the type of evidence presented. The clinical evidence is used to support claims with respect to relative effectiveness and safety of the health technology against the nominated comparator. In many cases, there may be multiple therapies being used in current practice, with different comparative profiles of benefit and cost relative to the new technology.

From a first-principles-approach, the comparator is the product most likely to be displaced, as this comparison provides an assessment of how the new technology compares in cost and outcomes to care being funded currently.

In Australia, the recommended comparator within the PBAC and MSAC Guidelines is the alternative that is most likely to be replaced with the introduction of the new intervention. The same definition of the comparator is also applied by England and Wales, Scotland, Canada, New Zealand, Norway, Japan, Singapore, and Taiwan.

However, in Australia, if the requested listing costs more than the alternative, the PBAC can only recommend if it is satisfied that the treatment provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)). The PBAC must provide a statement it is satisfied that this condition has been met in its recommendation. In practice this means that alternative therapies that are not the therapy most likely to be replaced may be relevant to the assessment for the purposes of pricing.

During the consultations conducted as part of the HTA Review in February 2024, concerns were raised by stakeholders pertaining to, among other matters, the comparator selection, particularly where the lowest price comparator is used. The feedback centred on concern that the choice of the lowest price comparator on the basis of Section 101(3B) (i.e., National Health Act 1953, Section 101(3B)) may result in the selected (lowest price) comparator being an older medicine with a low market share, and/or which may not constitute the current standard of care, such that the lowest cost comparator will not actually be replaced by the new intervention. HoweverSome of the written submissions noted they have no specific view with respect to price negotiation, and encouraged principles of early patient access and affordability to apply.

The PBAC and MSAC Guidelines also refer to selecting comparators that are currently funded treatments (i.e., PBS or MBS-listed) or standard medical management in the absence of a currently listed medicine/service for that same indication. Further to this, the MSAC guidelines explicitly state the expectation is that the chosen comparator is a health technology with established cost-effectiveness; and where the comparator is funded under a different source, and the cost-effectiveness of the comparator is unknown, the cost-effectiveness of both the comparator and the intervention may need to be established. Other jurisdictions, England and Wales, Scotland, Canada, New Zealand, and Norway recommended comparator for economic evaluation should be the one that is funded and used in routine practice/current care or as per the country's standard treatment guidelines.

It is also specified in some guidelines that the use of "no treatment" as comparator is accepted if this represents the most common clinical practice (e.g., by Norway and Sweden). France and Germany do not identify any specific definition of the comparator, instead recommend that all alternatives that compete with the intervention should be used as comparators. An example where there is a more explicit recommendation for the choice of comparator is Belgium, where the guidelines recommend the selection of the relevant comparator by using an efficiency frontier which involves identifying all relevant treatments or the targeted indication and population, the removal of dominated or extendedly dominated interventions from the list of relevant comparators, and the calculation of the ICERs for each intervention compared to the next best alternative. This method is also recommended in some other guidelines, e.g., the guidelines from Germany and France.

The PBAC Guidelines refer to the presentation of a near-market comparator where there is a reasonable expectation another medicine will enter the market. The SMC (Scotland) also have guidance for the considerations for near market comparators, where the submitting company

may need to consider whether a medicine that is currently being appraised by SMC or for which SMC has recently issued advice should be included as a comparator. The SMC also provide sponsors with guidance if the key comparator is available under a Patient Access Scheme (PAS), where medicines are made available under the ultra-orphan pathway for a three year period before a decision is made on routine use in NHS Scotland (see Part 2 Rare diseases and small patient populations).

A summary of guidance provided for the selection of comparators in HTA guidelines for each jurisdiction is provided in Table 10.

Table 10 Summary of the selection of comparators

Jurisdiction	Agency	Guidelines
Australia	PBAC	Comparator selection described on PBAC guidelines 2016 (pp13-14). PBAC bases judgement on main comparator. A current PBS listed medicine or standard medical management if the is no currently listed PBS medicine. Near market comparator.
	MSAC	Comparator selection described on MSAC guidelines 2021 (pp35-37) Therapeutic technology: • Current MBS-listed therapeutic technology and/or PBS-listed medicine(s) • Standard medical management (no treatment, placebo or sham treatment); Investigative technology • Current MBS-listed test (or multiple existing tests/test strategies) o If the proposed test is likely to replace an existing MBS-listed test, the relevant comparator would be the existing test. o If the proposed test is likely to be used in addition to an existing MBS-listed test, the relevant comparator would be the existing test with no additional testing, and the intervention should be the proposed test plus the existing test (or plus or minus the existing test if the proposed test is a triage test). • No testing and standard medical management – If the proposed test does not replace a current investigative technology, the comparator would usually be standard medical management and no testing.
England and Wales	NICE	Must be considered to be use in established practice for the population in the NHS. Can include technologies with no regulatory approval if considered to be part of an established NHS practice
Scotland	SMC	Relevant comparators are those that are considered to be in routine use or represent best practice in NHSScotland and are the treatments that are most likely to be replaced if the medicine under review is accepted by SMC. The submitting company may need to consider whether a medicine that is currently being appraised by SMC or for which SMC has recently issued advice should be included as a comparator. All relevant comparators identified; however also SMC guidelines also stated that a full comparison will not always be appropriate for every comparator. SMC provide guidance if the key comparator is available under a Patient Access Scheme (PAS).
Canada	CADTH	Should be technologies currently that the decision-making is currently funding and are commonly used. All interventions currently used and potentially displaced should be identified, in addition to interventions likely to be available in the near future. The inclusion of best supportive care (BSC) should be assessed for its appropriateness as a comparator where there is reason to believe that current technologies are of poor or uncertain value in comparison with BSC. This will allow decision-makers to note whether a technology appears more cost-effective as a result of being compared with a historically accepted technology of poor value.
New Zealand	PHARMAC	Should be the funded treatment(s) most likely to be replaced in New Zealand clinical practice and/or the treatment given to the largest number of patients (if this differs from the treatment most prescribers would replace).

Jurisdiction	Agency	Guidelines
		For vaccines: if an alternative vaccine is listed on the National Immunisation Schedule, this will usually be the main comparator. If there is currently no vaccine available, the main comparator would usually be standard medical management.
France	HAS	All comparators should be taken into account to build a cost-effectiveness frontier. Low utilisation of an intervention is not sufficient reason to justify its exclusion from the analysis if it is medically relevant. Comparators include interventions for which there is published clinical data, and health products for which there are published prices or maximum compensation amounts. The medicines under evaluation by EMA, and which meet those conditions, may be included if they are covered by a temporary usage authorisation (TUA), a post-TUA programme, or an early filing procedure with HAS. Medicines without a marketing authorisation (MA) may be used in the reference case analysis if they are widely used in common practice.
Germany	IQWiG	All healthcare-relevant interventions in a therapeutic area should be considered. An efficacy frontier is drawn on the basis of economic evaluation of interventions within a therapeutic area.
Norway	NOMA/ NIPH	The comparator is the alternative(s) which most probably will be completely or partially replaced if the intervention is taken into use. This will often be current established practice (for example, according to national guidelines) or the treatment which is most commonly used (number of patients). Comparators that have not been established to be cost-effective by NoMA are not usually adequate to show cost-effectiveness. These cases should be supported by an additional analysis e.g., against placebo, BSC, or an alternative therapy which can reasonably be assumed to be cost-effective. Comparators with a low cost and are viewed as established practice over a long period of time (with documented efficacy for the population) can be accepted as the comparator, but requires advanced clearance from NoMA. If it has been established by an earlier single technology assessment that the comparator is not cost effective, but it has still been used in clinical practice, then the analysis needs to be supported by an additional analysis as in the point above.
Sweden	TLV	The most cost-effective of the available and clinically relevant treatment alternatives in Sweden should be the comparison alternative. Clinical relevance means that the treatment is used in Swedish clinical practice and that the treatment is in accordance with science and proven experience. When there are no treatment options that are clinically relevant and cost-effective, the comparison option can be "no treatment".
The Netherlands	ZIN	Should be compared with the standard of care and/or usual care. The standard treatment is the intervention which in daily practice or in accordance with clinical guidelines is considered the treatment of first choice. Usual care includes care procedures which in clinical practice are routinely applied. If the standard treatment is not part of the usual care or cannot be defined, usual care procedures may be included in the analysis, whether or not next to the standard treatment. With respect to all interventions, the most recent national and international guidelines and standards should underlie the choice of the comparative intervention.
Belgium	KCE	All relevant comparators to be identified; the appropriate comparator is identified through construction of the efficiency frontier. Comparators for which there is no direct or indirect evidence should not be included in the economic evaluation. 'Off-label' pharmaceutical products can be used as valid comparators if there is evidence is available about the clinical safety and efficacy of the off-label use.
Japan	C2H	Comparator should be principally selected from technologies that are widely used in clinical practice and are expected to be replaced by the selected technology when it is introduced to treat the target population. Comparator should be selected from the technologies that can be used by public healthcare insurance except for when 'non-treatment' or 'watchful waiting' is appropriate. If a single comparator cannot be determined, the comparator should be selected by considering the comparators in RCTs, similar technologies for the official pricing, and cost-effectiveness based on agreement after consultation with C2H.
South Korea	HIRA	The comparator should be the drug with the highest market share among all comparable drugs. Comparators used in clinical trials can be selected as additional comparators if they meet the following conditions: 1) Recommended as standard

Jurisdiction	Agency	Guidelines
		treatments in medical practice; 2) No head-to-head evidence with the drug with the highest market share and the result of an indirect comparison is highly uncertain; and 3) Represent current practice in South Korea.
Singapore	ACE	The intervention that is most likely to be replaced by the technology under evaluation in local clinical practice or, in the case of add-on treatments, the current treatment without the technology added on. Comparisons with treatments which are used off-label for the indication under evaluation are allowed if they reflect common practice in the local setting
Taiwan	NIHTA (CDE)	The comparator can be what is most likely to be replaced by the drug in clinical practice. It can be another drug, a surgery, or no treatment. If a new medicine belongs to an existing category of medicines, the most frequently prescribed medicine in this category should be chosen as the comparator. If a new medicine belongs to a new category of medicines, and there are medicines of other categories used for the same indication, then the most frequently prescribed medicine among them should be chosen as the comparator.

ACE = Agency for Care Effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation (Taiwan); HAS = French National Authority for Health;; HIRA = Health Insurance Review and Assessment Service (South Korea); IQWiG = German Institute for Quality and Efficiency in Health Care (Germany); KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales (NICE)); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); UK= United Kingdom; ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).

Source: PBAC guidelines 2016; MSAC guidelines 2021; NICE guidelines 2022; SMC guidelines 2022; CADTH guidelines 2017; PHARMAC guidelines 2015; HAS guidelines 2020; IQWiG guidelines 2022; NoMA (pharmaceuticals) guidelines 2018; NoMA (medical devices and diagnostic interventions) guidelines 2021; ZIN guidelines 2016; KCE guidelines 2012; C2H guidelines 2022; HIRA guidelines (Bae et al.) 2022; ACE (medical technologies) guidelines 2022; ACE (drug and vaccine) guidelines 2021; CDE (TasPOR) guidelines 2006.

Why this matters?

All jurisdictions recommend a comparative assessment against current interventions. The criteria for selecting the comparator vary, but in most cases, it is guided by the therapy most likely to be replaced. Ensuring price alignment with comparators is crucial for maintaining cost-effectiveness. Australia recognises the role of opportunity cost by requiring consideration of comparison against not only the therapy most likely to be replaced but against the cost of other therapies. The PBAC can only recommend if it is satisfied that the treatment is, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)).

However, in practice this means that alternative therapies that are not the therapy most likely to be replaced may be relevant to the assessment for the purposes of pricing. There is a risk to sponsors/manufacturers in terms of being able to agree to a cost-minimising price. For Australia, this may result in sponsors having to resubmit to the PBAC once the cost-minimising price is known, or choose not to progress to listing.

HTA approaches to economic evaluation across jurisdictions

Economic evaluation provides a framework to systematically compare interventions so that all relevant alternatives are clearly identified, analysed and evaluated. The predominant economic evaluation approaches used in HTA are:

- Cost-minimisation analysis (CMA) (also known as cost-minimisation approach or cost comparison);
- Cost-consequence analysis (CCA);
- Cost-effective analysis (CEA);
- Cost-utility analysis (CUA); and
- Cost-benefit analysis (CBA).

CMA can be used where benefits/outcomes for the treatment are non-inferior to the comparator (i.e., the two interventions produce the same outcome and to the same magnitude). The overarching assumption underpinning CMA is that the therapeutic effects are the same between the treatments being compared, allowing the determination of an equi-effective dose (i.e., the doses required of the two therapies that produce the effects that are the same). For this reason, valuation of health outcomes is not included in the analysis; the key matter is whether the costs associated with two treatments required to produce those same effects differ. Where the treatments being compared are assessed as not differing (i.e., "equivalent") in terms of the benefits they provide, then interventions are cost-effective where the net cost is lower than the status quo. Issues arise in the conduct and interpretation of CMA where the therapeutic equivalence (i.e., equi-effective dose) is not demonstrated or established between the treatments being compared. The determination of therapeutic equivalence is based on acceptance of the clinical evidence presented, which is subject to the quality of evidence presented. Claims of non-inferiority are typically based on direct evidence: head-to-head randomised trials, pooled-analyses, and meta-analyses. In the absence of these types of evidence, indirect evidence including network meta-analyses, indirect treatment comparisons, single-arm studies, and matched-adjusted indirect comparisons (MAIC) have also been presented. A non-inferiority margin can be nominated to establish the minimal clinical important difference (MCID) between treatments where indirect evidence is presented i.e., the smallest difference for a particular outcome; noting that uncertainty in the treatment effect claimed arises with the decreasing strength of evidence.

CCA can be used to compare a range of costs and benefits/outcomes, which are presented in a disaggregated format when treatments are compared, without being expressed as a relative measure of effect (within treatment) or incremental effect (between treatments). This method allows for a broad range of costs and benefits/outcomes to be considered. Decision-makers are able to consider the relative importance of different costs and benefits/outcomes, and have flexibility in deciding which aspects of a treatment are most relevant to inform their decision. The drawback of CCA is that the rationale used to derive relative importance for decisions being made is not always clear.

In CEA the benefits/outcomes of two treatments can be expressed in the same non-monetary natural units (e.g., life years gained (LYG) or cases avoided), but the magnitude of their effects differs. Alternatives are evaluated in terms of their relative incremental costs per unit of that outcome as an ICER (e.g., cost ($) per LYG, cost ($) per case avoided).

CUA is a special case of CEA where the benefits/outcomes are expressed in terms of a measure that captures both morbidity and mortality impacts, typically QALYs. A QALY is a measure of health status and is derived by multiplying a QoL value by the quantity of life years.

In CBA costs and outcomes are valued and expressed in monetary terms from the perspective of those affected. It requires monetary valuation of the health outcomes of interest, potentially using methods such as willingness to pay (WTP). Healthcare payers are often reluctant to use CBA as the basis for reimbursement decision-making, largely due to the perception that explicitly placing a monetary value on a persons' life, as an example of a health outcome, is unethical. Moreover, there are distributional concerns with the CBA approach - it is thought that health gain should be valued equally regardless of the beneficiary or an individual's ability to pay. For these reasons, economic evaluation approaches within health care are dominated by CEA and CUA.

A summary of the approaches to economic evaluation discussed in the guidelines of the jurisdictions of reference is presented in Table 11. The subsequent sections provide further explanations of the methods pertaining to claims of improvement in efficacy or reduction in toxicity compared with alternatives employed by relevant agencies.

Table 11 Summary of preferred methods used for decision-making based on clinical claims across HTA agencies

Jurisdiction	Agency	Claims: Substantial improvement in efficacy or reduction in toxicity compared to alternatives?		Use of cost-effectiveness thresholds
		No claim	There is a claim	
Australia	PBAC and MSAC	CMA [a]	CUA (preferred)	No

Jurisdiction	Agency	Claims: Substantial improvement in efficacy or reduction in toxicity compared to alternatives?		Use of cost-effectiveness thresholds
		No claim	There is a claim	
			CEA CCA (supportive) [b]	
England and Wales	NICE	CMA/Cost comparison Faster process	CUA (preferred) CEA CCA (supportive) [b]	Yes
Scotland	SMC	CMA Faster process	CUA (preferred) CEA CCA (supportive) [b]	No
Canada	CADTH	CEA/CUA CMA (supplementary only where certain conditions are met)	CUA (preferred) CEA	No
New Zealand	PHARMAC	CMA	CUA (preferred) CEA	No
France	HAS	Assessment of added benefit	Preference unspecified: CUA, CEA; Assessment of added benefit	No
Germany	IQWiG	Assessment of added benefit	Assessment of added benefit	No
Norway	NOMA/NIPH	CMA	CUA (preferred) CEA	Yes
Sweden	TLV	CMA	CEA, CUA	No
The Netherlands	ZIN	CMA	CEA, CUA	Yes
Belgium	KCE	CEA/CUA is used to show health outcomes are identical prior to CMA being considered appropriate	CEA, CUA	Unclear
Spain	Various	Unclear	Unclear	No
Japan	C2H	CMA	Preference unspecified: CUA, CEA.	No
South Korea	NECA	Unclear	Preference unspecified: CUA, CEA.	No
Singapore	ACE	CMA Faster process	CUA (preferred) CEA	No
Taiwan	CDE	CMA	Preference unspecified: CUA, CEA.	No

ACE = Agency for Care Effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CCA = cost-consequence analysis; CDE = Center for Drug Evaluation (Taiwan); CMA = cost-minimisation analysis; CUA = cost utility analysis; HAS = French National Authority for Health; HTA = Health Technology Assessment; HIRA = Health Insurance Review and Assessment Service (South Korea); IQWiG = German Institute for Quality and Efficiency in Health Care (Germany); KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales (NICE)); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); UK= United Kingdom; ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).

There was no information pertaining economic evaluation approaches used formally by Spain.

Luxembourg does not have a formalised process for HTA.

a The PBAC guidelines refer to 'cost-minimisation approach', but is referred to as 'cost-minimisation analysis' for this report.

b Cost consequence analysis only used in the assessment of medical technologies by MSAC and NICE; and considered for ultra-orphan medicines by SMC.

Source: PBAC guidelines 2016 [1]; MSAC guidelines 2021 [2]; NICE guidelines 2022 [3]; SMC guidelines 2018 and 2022 [4, 5]; CADTH guidelines 2017 [6]; PHARMAC guidelines 2015 [7]; EUNetHTA guidance document 2015 [8]; HAS guidelines 2020 [9]; IQWiG guidelines 2022 [10]; NoMA (pharmaceuticals) guidelines 2018 [11]; NoMA (medical devices and diagnostic interventions) guidelines 2021 [12]; ZIN guidelines 2016 [13]; KCE guidelines 2012 [14]; C2H guidelines 2022 [15]; HIRA guidelines (Bae et al.) 2022 [16]; ACE (medical technologies) guidelines 2022 [17]; ACE (drug and vaccine) guidelines 2021 [18]; CDE (TasPOR) guidelines 2006 [19].

Where CEA or CUA are the preferred method, an incremental cost-effectiveness ratio (ICER) is derived that then must be used to assess value for money. Jurisdictions vary in how they evaluate the ICER. In some jurisdictions, a cost-effectiveness threshold is used to signal the maximum amount decision-makers are willing to pay for a unit of health outcome. England and Wales (NICE), Norway (NIPH/NoMA), and the Netherlands (ZIN) have explicit cost-effectiveness thresholds that provide a more structured framework for decision-making. While Australia has guidelines or considerations for cost-effectiveness, there is no explicit threshold that must be met for new interventions to be approved by PBAC or MSAC. Cost-effectiveness thresholds in the UK, the Netherlands, and Norway, can provide clarity and consistency in decision-making, but relies heavily on the utilitarian use and therefore agreed interpretation of the QALY across diseases, populations and other factors. This potentially limits the use of patient preference or social values in prioritising or weighting outcomes in the decision-making process. This limitation can be addressed by using weighted outcomes in these healthcare systems, allowing for the incorporation of factors such as severity of illness, patient preferences, or broader societal values, which may not be adequately captured by a single threshold.

Why this matters?
Evaluation methods used to inform product claims of non-inferiority or superiority in Australia are consistent with most of the jurisdictions reviewed. Australia (PBAC and MSAC) aligns with many agencies in adopting the perspective of the health care funder and relies on cost-effectiveness results from CUA/CEA to guide decision-making on health technologies. There is no specific cost-effectiveness threshold set in Australia. Establishing an explicit cost-effectiveness threshold would potentially limit consideration of the key factors for decision-making that reflect Australia's unique circumstances and priorities, societal values, and specific healthcare needs of the population.

Health technology claims of no difference

Methodological approach

Several HTA guidelines recommend CMA as the main approach that should be used where there is no claim by a sponsor of substantial improvement in efficacy or toxicity compared to the alternative(s) treatments i.e., non-inferior. These include, Australia, PBAC and MSAC; England and Wales, NICE; New Zealand, PHARMAC; Norway, NoMA and NIPH; Scotland, SMC; Sweden, TLV; France, HAS; Taiwan; Singapore, ACE; Japan, C2H; South Korea, HIRA. Although CMA is recommended by the PBAC and MSAC for health technologies claiming non-inferiority, the

PBAC and MSAC guidelines stipulate (PBAC Guidelines 2016 v5.0 p95; MSAC Guidelines 2021, p203) that if the AE profile of a proposed health technology and its comparator are significantly different in nature, it is unlikely a CMA will suffice, and recommend conducting a full economic evaluation to explore the impact on cost-effectiveness of differences in safety.

The CADTH guidelines (pp50-51) and SMC guidelines (p43) stipulate that CUA is the preferred approach for economic evaluation; however, CADTH and SMC stated that CMA can be conducted where certain conditions are met. For example, CADTH consider CMA appropriate where: 1) the drug is an additional drug in a therapeutic class where other drugs are currently reimbursed for the same indication; 2) the drug has similar clinical effects compared with the comparator i.e., has at least equivalent effectiveness and/or efficacy and be equivalently or less harmful. Clinical evidence must be based on one or more studies that directly compare the drug to the relevant comparator or an indirect comparison. The CADTH website/guidelines do not state whether evidence comparing single arms of trials or if subgroups from a trial are considered acceptable forms of evidence for use in CMA; and 3) the drug under review is anticipated to result in equivalent or lesser costs to the health system. Under these conditions, CADTH recommend CMA and CUA are both submitted for the review of a single indication (Procedures for CADTH Reimbursement Reviews, June 2023, p46).

The SMC guidelines state (p44) that “CMA may be appropriate if the proposed medicine is demonstrated by studies to be therapeutically equivalent to the relevant comparator(s), as assessed using an adequately designed and powered non-inferiority or equivalence or superiority study." The SMC prefer that analyses are based on final outcomes, but state that use of surrogate outcomes may be acceptable. Where a CUA shows extremely small differences between treatments in terms of QALYs, the SMC advise sponsors/manufacturers to provide sensitivity analysis showing the impact of assuming a CMA approach (i.e. no differences in QALYs). The SMC website/guidelines do not state whether evidence from a single arm or subgroups from a trial are considered acceptable.

The Norwegian guidelines (NIPH) [11] specify that adequate documentation (i.e., non-inferiority studies) is essential to show that the alternatives do have approximately identical effect if a CMA is to be used; The Belgian guidelines are consistent with the Norwegian guidelines. The PHARMAC guidelines (2020) recommend that appropriate levels of evidence should be identified; however well-conducted RCTs and meta-analyses are the preferred data sources when estimating relative treatment effects.

Pricing and price negotiations

There is variation across the jurisdictions with how price negotiation is handled, and at what time negotiations occurs within the HTA process. Pricing is implicitly included in the Australian HTA system in that while the PBAC does not negotiate price, it determines if a drug is of acceptable cost-effectiveness at a proposed price. The final price negotiation is between the sponsor and Government, occurring after a recommendation to list by the PBAC, and is initiated by the sponsor with the submission of a Notice of Intent for Pricing form and pricing offer package. The pricing negotiations that occur at this point are intended to ensure that the final price that is agreed between the sponsor and the Department is consistent with the PBAC advice. Once the Department has received the pricing package, there are guidelines for how long it takes to assess that the package documentation is complete (within 5 business days for package completeness). If not all the required information is provided, the missing information is requested from the sponsor. Once the pricing offer package is confirmed as complete, negotiation of the terms of listing commences.

There are issues with the assessment of costs for CMA, particularly with regards to comparator pricing. One issue is for comparators that have not been assessed in terms of their cost-effectiveness; using those as the basis to establish a price infers an acceptance that the comparator is cost-effective even though it has not been assessed as such. An example, might be for drugs in Australia listed outside of the PBS, such as drugs used in hospitals or treatments listed on the National Blood Authority (NBA), where existing prices have been established without regard to cost-effectiveness.

A second issue is that some drugs may be subject to specific commercial arrangements and have concealed' prices. In Australia, drugs with concealed prices include those where they are subject to a Special Pricing Agreement (SPA) or Risk Share Agreement (RSA), or those subject to price disclosure; similar arrangements apply in other jurisdictions. Where prices are not known, there is a risk to sponsors/manufacturers in terms of being able to agree to a cost-minimising price. For Australia, this may result in sponsors having to resubmit to the PBAC once the cost-minimising price is known, or choose not to progress to listing. For example, when the medicines are entering into the same therapeutic market as another medicine listed that is subject to a confidential deed of agreement, the applicant (i.e., sponsor/manufacturer) is required to give confidentiality undertakings (i.e., executed Deed of Confidentiality) before any confidential details of the deed of agreement are released to the applicant. This confidentiality process enables applicants to have access to information (e.g., effective price and other relevant information) required to determine if they would like to submit a Notice of Intent for

Pricing form. The applicant can choose to execute this step before they submit a Notice of Intent for Pricing form, or in parallel with the Notice of Intent for Pricing process (Procedure Guidance for listing medicines on the Pharmaceutical Benefits Scheme v2.5 pp45-46).

The current approach used in Australia for pricing of health technologies claiming non-inferiority is consistent with cost-equivalence rather than cost-minimisation; where cost-equivalence refers to net costs being maintained (i.e., at the same level), and cost-minimisation refers to the net costs being lower than associated with the comparator. The PBAC and MSAC guidelines state (PBAC Guidelines 2016, v5.0 p100; MSAC Guidelines 2021, v1.0 p205) that at the price requested, the overall cost of therapy with the proposed medicine should be the same as, or less than, the overall cost of therapy with the main comparator. Cost-equivalence is also practiced in Scotland where the SMC states (New Product Assessment Form 2022, p37) that the application needs to show the new medicine will: i) provide additional health benefits that are valued by patients compared to current Scottish practice and that this is at a net cost to the National Health Service in Scotland (NHS Scotland) that offers acceptable value in relation to other uses of the same resources; or ii) offer equivalent levels of health benefit to patients at an equivalent or lower net cost to the NHS Scotland. In both Australia and Scotland prices offered can be less than or equal to the comparator therapies. PHARMAC in New Zealand is one agency that practices cost-minimisation in their HTA processes. The PHARMAC guidelines states (PHARMAC Prescription for Pharmacoeconomic Analysis, 2015 p8), CMA assumes there is no net health change involved in moving from one treatment to another, so the decision is made on the basis of the difference in total cost alone. PHARMAC in New Zealand also conduct activities to support cost-minimisation including tendering processes and use of multi-product agreements [20].

CADTH have implemented a Streamlined Drug Class Review that aims to leverage published clinical information and provide timely evidence to support drug policy decisions and formulary management. The key factors for topic selection for the Streamlined Drug Class review include: 1) there is existing evidence (e.g., published meta-analyses) assessing the evidence of the effectiveness of the drug class; 2) the utilisation analyses demonstrate there may be an opportunity to improve optimal use; and 3) at least one of the drugs of interest has lost exclusivity (CADTH Streamlined Drug Class Review 2023, p2). The economic evidence presented as part of this process includes a cost comparison and a pan-Canadian budget impact analysis. The CADTH drug expert committees may specify that a recommendation in favour of reimbursement is contingent upon one or more conditions being satisfied. These conditions commonly include initiation criteria, renewal criteria, discontinuation criteria, prescribing

criteria, and conditions related to the price of the drug. Commonly used reimbursement conditions in reference to pricing conditions and cost considerations include (CADTH Procedures for CADTH Reimbursement Reviews, June 2023, p94, Table 21, pp94-95): 1) A reduction in price (i.e., cost-effectiveness must be improved); 2) That the cost of the drug under review not exceed the cost of the appropriate comparator(s); and 3) that the cost of the drug under review should provide cost savings compared with the appropriate comparator(s).

Internationally there are various methods that are used to price health technologies claiming non-inferiority; the three main methods described include:

- Internal reference pricing: Setting prices by referencing the prices of alternatives that are identical, similar, or therapeutically equivalent. Jurisdictions practising internal reference pricing include Australia, New Zealand, South Korea, and Japan. In Australia, the lowest price drug within the reference group is subsidised, and patients pay out of pocket costs for drugs that have a premium attached.
  In Australia, price disclosure arrangements were introduced as part of the PBS reforms package in 2006 [80]. Price disclosure is primarily used for drugs that lose exclusivity. Medications listed are allocated to a formulary identified as F1 (innovator/single brand) or F2 (generic/multiple brand) drugs [81]. Under the price disclosure program, manufacturers must submit sales information to the Department [82]. Where those sales data indicate that in-market sales are resulting in a price discount for a given molecule that is outside of an agreed margin, a weighted discount (based on the within market discounts) is applied to the PBS listed price. Price disclosure affecting F2 medicines will affect medicines seeking listing as an F1 formulary if the nominated comparator is an F2 medicine. In addition to the impact of price disclosure, drugs on both formularies are also subject to Statutory Price Reductions under Division 3A of Part VII of the National Health Act 1953 (the Act).

- International reference pricing: the prices of medicines in other countries are used to inform the price [83]. The number and selection of countries informing the international reference price, the calculation used to weigh price data, consideration of discounts applied, and how often the prices are revised, varies across the jurisdictions. The jurisdictions practising external reference pricing include France, Germany, Norway, the Netherlands, Belgium, Japan, Taiwan, South Korea [83, 84]. In South Korea, the determination of reimbursement is based on the price of seven countries (USA, Japan, Germany, France, Switzerland, UK, and Italy); in Japan, the prices are adjusted upward

or downwards to reflect the average drug price in four reference countries (UK, Germany, France, and the USA); Taiwan bases the referenced price on the median price for 10 jurisdictions (the UK, Germany, Japan, Switzerland, USA, Belgium, Australia, France, Sweden, and Canada).

- Tendering: a competitive bidding process where the government engage suppliers to submit quotes to be considered for the principal supply. New Zealand is one of the main jurisdictions that engages in tendering, describing the process on their website [20]. When medicines are no longer under patient, other suppliers are able to sell generic versions; the winning company becomes the principal supplier of the subsided medicine for a fixed terms (usually three years). Suppliers must be able to secure and maintain supply of the medicine. PHARMAC also consults with pharmaceutical suppliers on the list of products that are considered for inclusion in the annual multi-product tender. Suppliers are invited to submit Alternative Commercial Proposals for the supply of those products. PHARMAC then decides whether an Alternative Commercial Proposal offered by a supplier provides a better outcome than the likely outcome that might be achieved from tendering the product [20].

  Norway also engages in the tendering process for the procurement. The Norwegian Hospital Procurement Trust (Sykehusinnkjøp HF) is responsible for procurement of medicines for healthcare organisations. After completion of a single technology assessment, the Norwegian Hospital Procurement Trust conducts negotiations, tenders, and price agreements for new medicines that are financed by the hospitals, both for inpatients and outpatients. Subsequently a Decision Forum comprised of the four Chief Executive Officers (one from each Regional Health Authority) decides on whether to introduce the medicine or not. The main objectives of Norwegian Hospital Procurement Trust are to ensure equal and quick access to effective drugs, at the lowest possible price [85].

Process timelines

In Australia, all new drug submissions are evaluated within a 17-week cycle, this means that drug products claiming non-inferiority are processed using the same timelines as products claiming superiority. However, the time from first submission to PBS listing can be significantly longer than 17 weeks, as the evaluation cycle does not include the potential resubmission of evidence and modelling if a recommendation to list does not ensue. In addition to this time, the finalisation of pricing and budget impact is conducted with the applicant, the Department of Finance, and other government agencies, after the PBAC has recommended the medicine for

listing [21]. Applicants may also need to obtain internal approvals (i.e., from headquarters) prior to proceeding offer/acceptance of pricing. During the post-PBAC process of finalising the price, statutory price reductions need to be taken into consideration, and for some applications, confidential prices need to be disclosed to the applicant, where there is an additional process which is described on page 46 of the procedure guidance [21].

Two agencies have a faster process for assessment of products claiming non-inferiority compared with treatments claiming a substantial improvement (England and Wales, NICE; Singapore, ACE). The faster process is used for drugs in the same therapeutic class or the same compound with only a change in formulation.

ACE in Singapore conduct expedited evaluations for products claiming non-inferiority, of 2 to 3 months in duration (for products claiming superiority, evaluations are estimated to take between 6 to 9 months, and for vaccines the estimated timeframe is 6 to 12 months). An expedited evaluation is also considered for drugs with a lower budget impact (<SG$1 million per year) or which are available as a generic formulation of biosimilar. Finally, the extent of information available for evaluation and the availability of ACE technical resources to conduct the evaluation within the expected timeframe is taken into account when deciding whether an expedited evaluation is appropriate.

NICE have outlined two different methods using a proportionate approach including:

1) Cost comparison appraisals (formally known as ‘fast track approvals’). The cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. The newly streamlined approach shortened timelines by 45% to 23 weeks representing the time to positive recommendation. Recommendations are made by a subset of the committee outside of formal meetings, which differs from practice in Australia.
2) Streamlined decision-making - for technology appraisals that are beyond those suitable for cost comparison. Applies to evaluations that considered to be lower risk for patients, the NHS, stakeholders and NICE.

The NICE Guidelines (2022) stipulate that it is not possible to set absolute timelines for all stages of the evaluation, which is dependent on the nature of particular evaluations, as well as particular stages that coincide with public holidays.

The SMC implemented a fast-track resubmission process from January 2020 [86]. This process is only applicable for resubmissions where the only change is a new or improved simple PAS or if the point of the resubmission is a change to the confirmed price list. Resubmissions proceed directly to the SMC committee with an overall assessment timeline of up to 14 weeks i.e., there is no consideration by the New Drugs Committee (NDC). This resubmission process appears to be applicable for claims of non-inferiority and of superiority and appears to be similar for the Early Re-entry Pathway and Early Resolution Pathways, which are applied by PBAC [21].

In France, when innovation is claimed and potentially associated with a significant impact on health spending, health products and technologies are required to undergo a health economic evaluation. Added benefit claims are assessed on ASMR/ASA scale (I to IV). The website does not specify what process is undertaken if the technology does not provide an added benefit over the existing treatment being used as the comparator.

In Germany, a technical review is conducted in the first six months post listing. In the first three months of the HTA process, IQWiG evaluates the submitted evidence and shares their publicly accessible recommendation with the Federal Joint Committee (*Gemeinsamer Bundesausschuss* (G-BA)). Added therapeutic benefit is rated on a six-point scale (major, considerable, minor, non-quantifiable added benefit; no added benefit proven; benefit of the drug to be assessed smaller than benefit of the appropriate comparator therapy). The sponsor is then allowed to provide comments/feedback on this recommendation, and is provided with an opportunity to provide additional evidence. In the next 3 months, the G-BA conducts its HTA based on the sponsor's dossier, any additional evidence submitted by the sponsor, and the IQWiG recommendation, after which it publishes its final resolution on the additional benefit. The G-BA determines the additional benefit offered by the new medical intervention, based on the efficacy, safety or health-related quality of life demonstrated with the intervention versus a comparator therapy. The comparator is determined at the discretion of the G-BA, and reflects the current standard of care; it may be one specific treatment or a selection of treatment options. The G-BA rates the benefit through a combination of certainty, and magnitude ('extent') of the benefit, with 'No additional benefit (proven)' as a possible outcome.

Why this matters?
The timeline from the applicant's submission to PBAC decision-making is the same for technologies claiming non-inferiority and superiority. Two agencies, ACE and NICE, have a faster process for assessment of products claiming non-inferiority compared with those claiming superiority. ACE in Singapore conduct expedited

evaluations with an estimated timeframe of 2 to 3 months. Eligibility for expedited evaluations is based on budget impact, types of evidence presented, and the availability of the ACE technical resources team.

NICE (England and Wales) also allow for cost-comparison submissions if a health technology is likely to provide similar or greater health benefits at similar or lower cost. These are considered by a subset of the committee to expedite decision-making; however, the full committee must ratify that decision.

An expedited approach may provide faster access to the Australian market for products claiming non-inferiority with a minimal budget impact. This may require changes in the HTA processes and availability of a subset of PBAC members outside of scheduled times. However, the risks of reducing time may result in a loss of rigour in the evaluation in appropriately considering whether therapeutic equivalence has been met.

Health technology claims of a substantial improvement

For health technologies for which a sponsor claims superiority i.e., substantial improvement in efficacy or reduction in toxicity compared to alternatives, the recommended economic evaluation approaches were CEA and CUA. Differences in approaches across the jurisdictions were:

- CUA is the preferred approach in the reference/base case by: Australia, PBAC and MSAC; England and Wales, NICE; Scotland, SMC; Canada, CADTH; Norway, NoMA and NIPH; New Zealand, PHARMAC; Singapore, ACE.
- No preference for CUA and/or CEA was recommended; both approaches were considered acceptable; France, HAS; South Korea; Taiwan; Japan, C2H.
- Economic evaluation methods were not relied upon for decision-making in two jurisdictions (Germany and Spain).

If the main objective of the intervention is improving life expectancy and it does not have an effect on quality of life, some jurisdictions recommend a CEA with costs per life-years gained as the outcome measure (e.g., France, and the Netherlands). Other guidelines clearly state that a CUA should always be accompanied by a CEA with the costs per life-year gained as the outcome measure (Belgium, Norway, and Sweden).

Three agencies/committees consider the use of CCA for the evaluation of Medical Technologies (NICE and MSAC) and for ultra-orphan medicines (SMC). NICE's Medical Technologies Evaluation

Programme (MTEP) guidelines recommend CCA where high-quality economic evaluations are already available (MTEP 2017 pp40-41). The MTEP guidelines do not explicitly specify what should be included in the CCA; and states that the range of costs, resources, and clinical benefits included depend on the clinical characteristics of the individual medical technologies. The MSAC guidelines state (p161) that CCA should not be presented on its own. Since aggregated evaluations may obscure patterns of health care use or specific health outcomes, MSAC may request a CCA to be presented as a supplementary analysis to CUA and/or CEA (MSAC 2021, p161). The SMC guidelines state (p44) that CCA is not generally useful as the trade-offs between different dimensions of benefit are not made clear; however, SMC do state that they may consider CCA in the case of ultra-orphan medicines.

Why this matters?
CUA is the preferred approach taken in Australia (PBAC and MSAC) for products claiming superiority. This approach aligns with many agencies where CUA is relied upon to establish cost-effectiveness to guide decision-making on health technologies. It is not anticipated a move away from the use of CUA would result in an improvement to the HTA system.

Conclusion

Australia is one of the 12 jurisdictions that formally use economic evaluation in decision-making (Australia; England and Wales; Scotland; New Zealand; Canada; The Netherlands; Belgium; Norway; Sweden; Singapore; South Korea; Taiwan). There are some key differences in the way HTA systems are set up across jurisdictions pertaining to perspective taken in analyses, recommendations with respect to the economic evaluation approaches taken, and the use of thresholds.

The approach taken by Australia is consistent with most agencies, where the perspective of the analysis being that of the health care funder and there is a reliance on CUA/CEA to inform cost-effectiveness for health technologies. Only a few agencies explicitly use thresholds to determine cost-effectiveness (NICE; NIPH/NomA; ZIN), which can provide some transparency in decision-making. While PBAC and MSAC consider cost-effectiveness, there is no explicit threshold that is applied. The lack of an explicit threshold in Australia, allows greater flexibility by decision-makers (in terms of what else is considered outside of the ICER); however, the flexibility is at the cost of transparency and uncertainty when establishing price setting.

There is consistency across most of the jurisdictions in the recommendation for comparator selection (PBAC; MSAC; NICE; CADTH; SMC; CADTH, PHARMAC, NIPH/NoMA; C2H; ACE; CDE)

which state that the comparator should be the alternative that is most likely to be replaced with the introduction of the new intervention. In Australia, if the requested listing costs more than the alternative, the PBAC can only recommend if it is satisfied that the treatment is, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)). The PBAC must provide a statement it is satisfied that this condition has been met in its recommendation. In practice this means that alternative therapies that are not the therapy most likely to be replaced may be relevant to the assessment for the purposes of pricing. Concerns were raised by stakeholders pertaining to, among other matters, the comparator selection, particularly where the lowest price comparator is used. The feedback centred on concern that the choice of the lowest price comparator on the basis of Section 101(3B) (i.e., National Health Act 1953, Section 101(3B)) may result the selected (lowest price) comparator being an older medicine with a low market share, and/or which may not constitute the current standard of care, such that the lowest cost comparator will not actually be replaced by the new intervention. However, 101(3B) does not require that the lowest priced medicine be used as the comparator if it is accepted as being inferior. The PBAC can and has accepted evidence that potential lowest price comparators are not alternative therapies because they were inferior for some patients, or were no longer considered in clinical practice as alternative therapies. In other instances the PBAC has considered that a therapy proposed for listing should be cost-minimised to an alternative therapy that is not the most likely to be replaced where it is satisfied that the alternative therapy is non-inferior to the therapy proposed for listing.

CMA is an accepted approach to economic evaluation across many jurisdictions (Australia, PBAC and MSAC; UK NICE; New Zealand, PHARMAC; Norway, NoMA and NIPH; Scotland, SMC; Sweden, TLV; France, HAS; Taiwan; Singapore, ACE; Japan, C2H; South Korea, HIRA), where products have no claims of substantial improvement in efficacy or reduce toxicity compared to alternatives (i.e., non-inferiority).

In Australia, all new drug submissions are evaluated within a 17-week cycle, this means that drug products claiming non-inferiority are processed using the same timelines as products claiming superiority. However, the time from first submission to PBS listing can be significantly longer than 17 weeks; considering potential for rejection and resubmission of evidence and/or revised modelling, and additional processes that occur after the PBAC decisions are made. Two agencies have a faster process for assessment of products claiming non-inferiority compared with treatments claiming a substantial improvement (England and Wales, NICE; Singapore, ACE). For both of these agency's processes budget impact is a factor considered. ACE have

outlined set times in their guidelines, noting that CMAs are conducted within 2-3 months; and expedited evaluations are considered for drugs based on budget impact (<SG$1 million per year) or which are available as a generic formulation of biosimilar. The cost comparison process used by NICE is an expedited process is used for a health technology that is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication.

Weighting of health outcomes and risks/harms

Value assessment frameworks used in decision-making by HTA agencies reflect a range of social values with respect to the therapeutic benefits of a technology and their broader social impact [25]. Various methods have been used to try to reflect those social values and to understand how health outcomes, risks and harms might be weighted in affecting decisions in HTA. In this section, how those weights have been determined and applied in HTA in relation to health outcomes and risks/harms is discussed, with a focus on the use of weighted scales, patient relevant outcomes, patient preferences, and indirect and non-health benefits.

A summary of the methods applied across jurisdictions for the weighting of health outcomes and risk/harms in informing HTA decision-making is provided in Table 12. In Australia, utility weights used in economic modelling, however other methods for QALY weighting are not typically used. Qualitative MCDA is also used by the PBAC and the MSAC where key factors influencing decision-making is outlined the guidelines; and explicit or quantitative weights are not applied to key factors.

Table 12 Methods for weighting of health outcomes and risks/harms

Method	Point of application within HTA		Comments/reasons for application
	Decision-making process	Modelling	
MCDA	Yes: committee deliberation	No	Also referred to as Analytic Hierarchy Process used in Germany.
Conjoint analysis DCE MAUI	 Possible Possible	 Possible Yes	DCE methods are discussed in the literature with possible applications in HTA.
TTO	No	Yes	Utility weights used in modelling
SG	No	Yes	Utility weights used in modelling
QALY weighting	No	Yes	Shortfall method e.g., severity modifier. Used by England and Wales (NICE), Norway (NoMA and NIPH), The Netherlands (ZIN). Caregiver e.g. Sweden (TLV)
Friction cost approach (FCA)	No	Yes	Economic evaluation using societal perspective
Human capital approach (HCA)	No	Yes	Economic evaluation using societal perspective

DCE = Discrete Choice Experiment; FCA = Friction cost approach; HCA = Human capital approach; HTA = Health Technology Assessment; MAUI = multi-attribute utility instruments; MCDA = multicriteria decision analysis; NICE =

National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; QALY = quality adjusted life year; SG = Standard Gamble; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); TTO = time trade-off; ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).

Classically, HTA focuses on the clinical, economic, and financial implications of adding a new health technology for listing; however, social and ethical implications may also be considered important/significant for decisions being made.

The most widely used economic evaluation approach is to value health benefit using the QALY. This approach has been criticised for neglecting societal preferences that may prioritise certain individual groups health gains over others, thereby overlooking considerations of equity [22] [23]. In response to the apparent equity limitations of applying the QALY, different approaches have been suggested for operationalising the equity-efficiency trade-off [22] [24].

a. Weighted scales

There are a few methods used in HTA which rely on the application of weighted scales of health outcomes and risks/harms. These methods include MCDA, and the stated preference methods of CA and DCEs. These methods allow relative weights to be assigned to different health outcomes and health care services to reflect their importance as part of decision-making.

MCDA has been described as a structured way to include varying aspects of the social values held in society [25]. MCDA is a method used to evaluate the overall value of interventions in reference to prespecified criteria [87]. A range of criteria may be considered including health and non-health benefits, which may be quantitative or qualitative in nature. In using this approach, a decision is made based on the relative importance of each criterion in affecting a decision. MCDA processes includes at least three steps; 1) defining the decision problem; 2) selecting criteria which reflects values; and 3) construction of the performance matrix outlining the set of generic criteria for decision-making. Different forms of MCDA have been described by Baltussen et al (2019) encompassing ‘qualitative MCDA’, ‘quantitative MCDA’, and ‘MCDA with decision rules’:

- Qualitative MCDA: is where a committee passes judgement on the overall value through deliberation using explicit criteria. An advantage of this approach is that where explicit criteria underpin decision-making, those criteria must be considered comprehensively, fostering transparency on which criteria are considered (but not their weightings) and consistency with respect to decision-making. The disadvantages of qualitative MCDA include dominance by some voices over others (unless mechanisms are in place to minimise dominance); and a lack of transparency on how criteria are

weighted, as decision makers make implicit judgments on the weights of the criterion proposed e.g., Thailand [88].

- Quantitative MCDA: in quantitative MCDA, a value function is specified for stakeholders (healthcare providers, patients, citizens, funders, and decision makers); elicitation of stakeholder preferences is conducted to ascertain relative importance of the criteria which may be based on methods using the AHP or DCE; a 'value measurement model' is used to sum the weighted scores and obtain an overall value for each technology. Uncertainty analysis is conducted on these weighted results, which are presented to HTA committees for deliberation based on the rank order. Rank ordering may change during committee deliberation. Quantitative MCDA is criticised for being mechanistic, ignoring opportunity costs, and not following best practice guidelines; consequently this approach has been rejected by some HTA agencies (England and Wales, NICE; and The Netherlands, ZIN) [25].
- MCDA with decision rules (i.e., structured deliberation): is where a committee uses a simple set of decision rules to interpret a performance matrix, which guide the trade-offs being made between the explicit criteria. This approach is used by England and Wales (NICE) and The Netherlands (ZIN) where equity weighting or modifiers are applied directly to a QALY (i.e., weighted QALY) e.g., for severity and decision modifiers.

Stated-preference methods, such as conjoint analysis, can be used to identify and evaluate the relative importance of aspects of decision-making related to health outcomes, risks and harms, and of health care services [89] [90]. Conjoint analysis and DCEs are survey-based methods used to capture preferences for underlying features that can be factored into decision-making. Conjoint analysis can take various forms, however specific forms discussed in HTA guidelines and websites were in relation to the AHP. DCEs are a method of eliciting stated preferences from respondents through a structured survey that presents respondents with a series of choice tasks [91] [92]). DCE methods have been used to elicit preferences for features of the Australian health care system, where attributes representing level of health, equity, responsiveness and healthcare financing were considered [93].

There are challenges that arise when using stated preference methods for weighting decision factors in HTA. Results from DCEs are occasionally viewed with some scepticism as the method relies on hypothetical choices and, consequently, has been criticised for lacking external validity [89]. As an example, bias in results may arise if choice tasks do not adequately reflect real-life decision-making, such as when an important characteristic of a matter subject to choice (an attribute) that could potentially influence a respondent's choice is not included. Results of a

DCE may also be biased when participants do not have clear preferences, or when participants feel compelled to exaggerate or downplay the significance of particular attributes due to perceived interests [89]. Developing a set of weights acceptable for decision-making may be problematic where flexibility is needed, particularly for where there are important differences in values relating to health outcomes and other factors considered in decision-making. In addition, those weights may change with different decision contexts such that establishing an acceptable set of generalisable decision weights a-priori is challenging.

Comparisons of HTA processes across jurisdictions

The methods and processes for weighting outcomes discussed in several HTA agency guidelines and websites are summarised in Table 13. The subsequent sections provide detailed explanations of the methods and processes employed by those relevant agencies.

The use of outcome weighting in decision-making processes varies across jurisdictions. Five of the jurisdictions explicitly utilise methods such as MCDA, stated preference methods, and QALY weighting (England and Wales (NICE); The Netherlands (ZIN); Norway (NIPH); Sweden (TLV); Germany, (IQWiG)). Although not explicitly stated, four of the counties appear to use qualitative deliberation for decision-making (Australia (PBAC/MSAC); New Zealand (PHARMAC); Canada (CADTH); Scotland (SMC)).

Table 13 Consideration of weighting of decision factors across jurisdictions and HTA agencies

Jurisdiction (HTA agency)	Mentioned in the guideline	Method used for weighted scales	Application
Australia (PBAC, MSAC)	No (not explicitly)	Qualitative deliberation: In making recommendations the PBAC/MSAC apply judgements to value health technologies during deliberation.	PBAC does not explicitly apply weighing to outcomes in economic modelling. However, other less-readily quantifiable factors that also influence PBAC decision-making are outlined (PBAC Guidelines v5.0 pp4-5). [Consultation – consumer/patient groups; Submission can provide additional evidence in the form of expert opinion (PBAC Guidelines v5.0 Appendix 1)].
England and Wales (NICE)	Yes	Structured deliberation: MCDA applied with decision rules. (1) MCDA (2) Decisions modifiers; proportional shortfall and absolute shortfall	MCDA: To support cost–consequences analysis when a cost per QALY approach is not possible Decision modifiers (severity and size of benefit): When QALY do not factor in all benefits, because they cannot be, and value judgements. Modifiers can be taken into account qualitatively through committee discussion or quantitatively.
Scotland (SMC)	No (not explicitly)	Qualitative deliberation.	SMC do not explicitly apply weighing to outcomes. However, other factors are considered that can also influence decision-making.

Jurisdiction (HTA agency)	Mentioned in the guideline	Method used for weighted scales	Application
			An additional QALY is of equal value regardless of individual characteristics such as their socio-demographic details, or their pre- or post-treatment level of health end-of-life/rare medicines.
Canada (CADTH)	Not explicitly specified	Qualitative deliberation. In the reference case, all outcomes should be weighted equally, regardless of the characteristics of people receiving, or affected by, the intervention in question	However, it allows for weighting of health outcomes to consider distributional and equity-related policy concerns.
New Zealand (PHARMAC)	No (not explicitly)	Qualitative deliberation. Health-related benefits included in a cost-utility analysis should not be weighted	PHARMAC do not explicitly apply weighing to outcomes in economic modelling. Factors outlined for consideration for decision-making by PHARMAC are: need, health benefits, suitability, and costs and savings.
France (HAS)	No	-	Weighting of QALYs according to the individual characteristics of the persons involved in the intervention (socio-demographic factors, severity, etc.) is not recommended.
Germany (IQWiG)	Yes	Quantitative deliberation: Analytic hierarchy process (AHP) and discrete choice experiments (DCE).	Determination of preferences to establish a measure of overall benefit.
Norway (NIPH/NoMA)	Yes	QALY weighting Similar to NICE, according to absolute shortfall of QALYs. Variable threshold.	Factors considered: equal access, need, and solidarity, aiming to ensure fairness and equity in resource allocation. For prevention and severe diseases.
Sweden (TLV)	Yes	QALY weighting using severity (note: severity is not clearly defined) Variable threshold.	Caregivers QoL included in economic evaluation (reference case for ATMPs,). Principles of human dignity, need, cost-effectiveness, and solidarity, allocating resources based on need and considering factors such as illness severity, patient preferences, and societal values alongside cost-effectiveness.
The Netherlands (ZIN)	Yes	DCE and MCDA (directly consulting patients and users). References the NICE Diagnostic Assessment Programme. Proportional shortfall method. Variable threshold.	Principles of human dignity, need, cost-effectiveness, and solidarity, allocating resources based on need and considering factors such as illness severity, patient preferences, and societal values alongside cost-effectiveness. In the Netherlands for diagnostic test to identify other value components (which were not specified in the guidelines)
Singapore (ACE)	No (not explicitly)	Qualitative deliberation: In making recommendations the committees apply judgement to value health technologies.	ACE does not explicitly apply weighting to health outcomes in economic modelling. Factors outlined for consideration for decision-making by the committees are: Clinical need of patients, clinical effectiveness, safety and cost-effectiveness of the technology, and budget impact. Additional factors, including social, cultural and ethical issues, and other value judgements may also inform their considerations.

ACE= Agency for Care Effectiveness; AHP= Analytic hierarchy process; ATMPs= Advanced therapy medicinal products; CADTH= Canadian Agency for Drugs and Technologies in Health; DCE= Discrete choice experiment; HAS = French National Authority for Health; HTA= Health technology assessment; IQWiG = Institute for Quality and Efficiency in Health Care (Germany); MCDA= Multicriteria decision analysis ; MSAC= Medical and Scientific Advisory Council; NICE= National Institute for Health and Care Excellence; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; QALY= Quality adjusted live year; SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; UK= United Kingdom; ZIN= The National Health Care Institute.
There was no information pertaining to the use of weighting of decision factors specified by these jurisdictions (Belgium; Luxembourg; Spain; Japan; South Korea; Taiwan).
Source: ACE guidelines 2023; C2H guidelines 2022; CADTH guidelines 2017; HAS guidelines 2020; IQWiG guidelines 2022; KCE guidelines 2012; MSAC guidelines 2021; NICE guidelines 2022; NoMA guidelines 2018; PBAC guidelines 2016; PHARMAC guidelines 2022; SMC guidelines 2022; TLV guidelines for precision medicine 2022 and ZIN guidelines 2016.

In the HTA agency guidelines reviewed, three general approaches to the weighting of health outcomes for decision-making have been identified. One approach applies equity weights to QALY gains and evaluates the adjusted ICER against a fixed monetary threshold value (England and Wales (NICE)). A second approach evaluates an unadjusted ICER against a flexible monetary threshold value (Norway (NoMA) and The Netherlands (ZIN)). A third approach is qualitative deliberation where no explicit weighing of QALYs is done (i.e. Australia (PBAC, MSAC). In this regard, New Zealand (PHARMAC) states that the HTA is a deliberative process informed by quantitative models, but they are not deterministic. Decision-makers can choose how much and how to weight quantitative and qualitative results to arrive to a decision. Submissions should provide as much information as possible regarding indirect and non-health benefits while the deliberative process of HTA has to be flexible enough to consider these.

Severity of a health condition and QALY weighting

Four jurisdictions (England and Wales (NICE); The Netherlands (ZIN); Norway (NIPH); Sweden, (TLV)) have operationalised the weighting of QALY by including severity of disease as one of the factors to consider in the decision-making process. The estimation of the severity of a health condition involves using the concept of QALY shortfall in the Netherlands (ZIN), Norway (NIPH/NoMA), and England and Wales (NICE). However, the approach to defining severity differs between these jurisdictions.

- England and Wales (NICE): uses both the Absolute Shortfall and Proportional Shortfall methods, noting that the higher severity level will apply. The aim is to establish a comprehensive and broad definition of severity[3]. These scores are incorporated into NICE's new severity modifier (published in January 2022).

[3] NICE stated in the "Review of methods for health technology evaluation programmes: proposals for change" (2021) that "in the absence of evidence for specifying severity weights, our current approach takes an "opportunity cost neutral" analysis to severity, that is our basic principle aims to reallocate the weights applied to incremental QALYs currently invested in end-of-life treatments to those for severe disease". However, it recognised the need for research as soon as possible aiming to generate evidence to further inform: (a) the degree to which society favours severe diseases considering the health benefits that might be displaced as a consequence and (b) the QALY weighting that should be applied.

- Absolute Shortfall score: represents the absolute number of future QALYs lost by individuals living with a particular disease. Using this approach means younger patient populations have a higher number of potential future QALYs to lose on average. As a result, chronic diseases affecting younger populations may receive higher Absolute Shortfall scores compared to severe acute diseases that primarily affect older populations.
- Proportional Shortfall score: represents the proportion of future QALYs lost by individuals living with the disease. Older or elderly patient populations, who are closer to the end of their lives, have relatively fewer potential QALYs left on average. Consequently, they are more likely to lose a higher proportion of their remaining QALYs due to a severe disease, leading to higher Proportional Shortfall scores on average.

The NICE guidelines state that deviating from the reference case and applying modifiers should be morally and ethically supported by reason, coherence, and available evidence. The application of the severity modifiers is used for technology appraisals, and not for technologies evaluated through the Medical Technologies Evaluation Program, diagnostic evaluations, or for technologies reviewed under the Highly Specialised Technologies Program (NICE Manual 2022: 6.2.13, 6.2.20). NICE considers that the QALY weights are unlikely to reflect the societal value and severity of disease in a way that is unlikely to reflect the societal value and severity of disease in a way that is relevant to the diagnostics context (p165). NICE considers that the severity of the condition is already implicitly captured in the selection of technologies for products being evaluated in the HST program (p165). For technology appraisals, the maximum acceptable ICER ranges between £20,000 to £30,000 per QALY gained, whereas cost effectiveness of highly specialised technologies is £100,000 cost per QALY gained. The NICE health technology evaluations manual (2022) further specifies that technologies that are recommended after application of the severity modifiers will be considered as the relevant comparators for future evaluations of new technologies introduced for the same condition.

- Norway (NIPH/NoMA): relies solely on Absolute Shortfall for estimating severity and considered that the Proportional Shortfall lacks a lifetime perspective and does not adequately account for the size of future losses [94]. Higher weights are assigned to conditions with greater Absolute Shortfall of QALYs. These weights are used to determine the acceptable cost per QALY threshold for specific health conditions.

Patients with more severe conditions receive higher priority in accessing treatment. Severity is quantified as the decrease in prospective healthy life years compared to the healthy life expectancy of individuals without the disease.

- The Netherlands (ZIN) uses the Proportional Shortfall method to allow for higher costs per QALY for severe illnesses, with the threshold varying depending on the Proportional Shortfall. The proportional shortfall in the ZIN guideline is based on the 'Global Burden of Disease' data from the World Health Organization (WHO).

While all three jurisdictions apply notionally the same approaches in terms of absolute or proportional shortfalls, how those are made operational and the implication for decision-making differs (e.g., cut-offs for proportional shortfalls differ); see Table 14.

Table 14 Comparison of QALY weighting across the Netherlands (ZIN), Norway (NIPH/NoMA) and England and Wales (NICE)

Criteria	Netherlands (ZIN)		Norway (NIPH/NoMA)		England and Wales (NICE)	
	Proportional Shortfall (PS) (QALY)	Threshold (€/QALY)	Absolute Shortfall (AS) (QALY)	Threshold (NOK/QALY)	Shortfall (PS and AS) (QALY)	QALY weight
Proportional Shortfall						
Low	0.1–- 0.4	Up to 20,000			<0.85	x1
Medium	0.41–- 0.7	Up to 50,000			0.85–- 0.95	x1.2
High	>0.71	Up to 80,000			>0.95	x1.7
Absolute Shortfall						
Low			0– 15	<250,000	<12	x1
Medium			16– 30	<500,000	12 – 18	x1.2
High			31– 45	<750,000	≥18	x1.7

NoMA= Norwegian Medicines Agency; NICE= National Institute for Health and Care Excellence, ZIN= The National Health Care Institute. AS= Absolut shortfall; NICE= National Institute for Health and Care Excellence; NIPH= Norwegian Institute of Public Health; NOK= Norwegian Kroner; NoMA= Norwegian Medicines Agency; PS= Proportional shortfall; ZIN= The National Health Care InstituteNOK

NOK= Norwegian Kroner. 250,000 NOK ≈ 28,000 EUR ≈ 31,250 AUD ≈ 25,000 GBP. 500,000 NOK ≈ 57,000 EUR ≈ 62,500 AUD ≈ 50,000 GBP. 750,000 NOK ≈ 85,000 EUR ≈ 93,750 AUD ≈ 75,000 GBP. 1,000,000 NOK ≈ 110,000 EUR ≈ 125,000 AUD ≈ 100,000 GBP (as of July 12, 2023).

Source: NICE guidelines 2022, NoMA guidelines 2018 and ZIN guidelines 2016.

The TLV in Sweden takes a clear departure from both Absolute Shortfall and Proportional Shortfall measures. In Sweden, severity is not consistently measured using QALY shortfall, primarily due to the influence of the Human Dignity Principle, which prohibits taking chronological age into account. This principle has been interpreted as a barrier to adopting an absolute shortfall approach to severity in Sweden [26]. Although the TLV does not have an explicit cost-effectiveness threshold, a review by Barra et al [26] indicate that drugs with are approved at a higher cost-effectiveness threshold based on the severity of a condition. The TLV acknowledges that treatments for severe conditions may result in higher costs per QALY than treatments for milder conditions. However, the criteria applied by TLV for categorising a disease as severe have not been explicitly defined. The TLV apply different ICER thresholds for health

conditions judged to be qualitatively more severe. A review of Swedish HTA decisions up to 2019 showed acceptable thresholds for different levels of severity [26]:

- For the most severe conditions, the acceptable threshold is up to 1 million Swedish krona (SEK) per QALY gained (approximately AUD 140,000).
- For severe conditions, the threshold is 750,000 SEK (approximately AUD 105,000) per QALY gained.
- For moderate conditions, the threshold is 500,000 SEK (approximately AUD 70,000) per QALY gained.

Strictly speaking, the consideration of severity in Norway (NIPH/NoMA) and the Netherlands (ZIN) is applied to the cost-effectiveness threshold. However, in practice, this can be understood as a form of weighting of the QALY gain.

Case study: Reimbursement Decision for a hypothetical drug

A pharmaceutical company has developed a novel drug called "Vitexin" designed to treat a genetic disorder called "Zygotis Syndrome". Zygotis Syndrome affects a small population of patients, making it a rare disease. Vitexin is a breakthrough medication that has demonstrated significant improvements in the quality of life for patients with Zygotis Syndrome.

The company has applied for reimbursement of Vitexin in three different jurisdictions: the Netherlands (ZIN), Norway (NIPH/NoMA), and England and Wales (NICE). Each jurisdiction has its own reimbursement criteria based on either Proportional Shortfall (PS) or Absolute Shortfall (AS) of QALYs. Hypothetical reimbursement decisions in each jurisdiction are as follows:

- The Netherlands (ZIN): the ZIN follows the Proportional Shortfall approach. Zygotis Syndrome is considered a "High" severity condition, with a Proportional Shortfall in QALYs exceeding 0.71. According to ZIN's criteria, drugs for "High" severity conditions can be reimbursed at a threshold of up to €80,000 per QALY. Vitexin, has an estimated cost-effectiveness ratio of €70,000 per QALY compared to standard of care. Therefore, based on the Proportional Shortfall criteria , Vitexin would likely be recommended for reimbursement since it falls below the €80,000 threshold.
- Norway (NIPH/NoMA): the Absolute Shortfall approach for reimbursement decisions. For "High" severity conditions, the AS threshold is set at a QALY shortfall

of ≥18. Vitexin results in a QALY shortfall of 16, which is just below the threshold of 18. However, Norway's AS threshold also considers a cost limit of <750,000 NOK per QALY. Vitexin's cost-effectiveness ratio is 800,000 NOK per QALY. Under Norway's Absolute Shortfall criteria, Vitexin would not meet the reimbursement criteria due to its high cost.

- England and Wales (NICE): NICE evaluates reimbursement using both Proportional Shortfall and Absolute Shortfall criteria. For "High" severity conditions, the Proportional Shortfall threshold is set at >0.71, and the Absolute Shortfall threshold includes a QALY shortfall of ≥18. Vitexin meets the Proportional Shortfall criteria since it has a high QALY improvement. However, like Norway, NICE also considers a cost-effectiveness threshold, which is £50,000 to £70,000 per QALY gained. Vitexin's cost-effectiveness ratio falls within this range. Therefore, under NICE's combined criteria, Vitexin is likely to be recommended for reimbursement.

The reimbursement decision for the hypothetical drug Vitexin can vary significantly depending on whether the country's healthcare authority considers Proportional Shortfall or Absolute Shortfall of QALYs. In this case study, while the Netherlands and England and Wales are likely to recommend reimbursement based on Proportional Shortfall criteria, Norway would not recommend reimbursement due to high costs based on Absolute Shortfall criteria.

Flexibility in the decision-making process

The QALY weighting approach (either through the use of multipliers applied directly to QALYs gained or through the use of variable threshold) explicitly factors severity of illness to allow for greater consideration or priority in resource allocation decisions, which can provide some structure and consistency in reimbursement decision-making. However, weighting health outcomes can potentially limit flexibility and adaptability of a deliberative process due to [95] [96] [97]:

- Simplified and narrow assessment: when weighted outcomes are used, decision-making tends to focus on the factors being weighted. This can lead to oversimplification of complex healthcare issues and a narrow assessment of the value and impact of different interventions or treatments. By relying on weighted outcomes, a deliberative process using decision rules e.g. severity, may fail to consider the full range of relevant factors and perspectives, limiting its flexibility and adaptability.

- Limited stakeholder input: in a deliberative decision-making process, stakeholder engagement and input play a crucial role in ensuring a fair and inclusive approach. However, the use of weighted outcomes can potentially marginalise certain stakeholders or perspectives. If the weighting is based on preconceived notions or biases, it may disproportionately favour certain groups or conditions, overlooking the voices and needs of others. This restriction on stakeholder input undermines the flexibility of the process and hampers its ability to adapt to changing societal values and priorities.
- Lack of contextual consideration: weighted outcomes often rely on predetermined weights assigned to specific health conditions or interventions. However, the value and impact of healthcare interventions can vary in different contexts, such as patient populations, healthcare settings, cultural norms, or can change over time. The use of weighted outcomes can hinder the flexibility of decision-making if those weights do not account for the preferences of the relevant population where the reimbursement decision is being taken.
- Resistance to new evidence or changing priorities: a deliberative decision-making process should be open to incorporating new evidence and adapting to changing societal values and priorities. However, the use of weighted outcomes can create rigid decision-making frameworks that are resistant to updating or revising the assigned weights. This can impede the incorporation of new scientific findings, shifts in public opinion, or changes in healthcare priorities. The lack of flexibility to adapt to evolving circumstances undermines the effectiveness and responsiveness of the decision-making process.

While the use of weighted outcomes can simplify the deliberative process, there is a risk of overlooking other factors that can be considered using a more flexible decision-making process. This rigidity in decision-making may impede the ability to adequately address distributive issues and adapt to evolving circumstances. An exclusive reliance on cost per QALYs in the decision-making process, for example, may result in neglecting important distributional considerations. While QALYs provide a standardized measure for comparing health outcomes, they may not fully encompass the impact of certain conditions or populations.

To address limitations associated with explicitly weighting outcomes, qualitative deliberation is incorporated into the decision-making process alongside the use of QALYs in some jurisdictions (Australia, PBAC and MSAC; New Zealand, PHARMAC; Canada, CADTH). This approach enables

consideration of various factors beyond estimated health outcomes alone, leading to a more nuanced analysis of the impact of resource allocation decisions on different population groups and their specific needs.

An example of a flexible decision-making process can be seen in New Zealand. The PHARMAC guidelines in New Zealand [7] recommend using QALYs in the assessment of health benefits for cost-utility analysis. However, they advise against incorporating other aspects such as health need or disease severity when estimating HRQoL Therefore, the guidelines recommend not introducing additional weightings when calculating QALYs, or adjusting their weighting to reflect value judgments related to distributive justice, factors like disease severity or distributive justice, respect for autonomy, or health need. Instead, the guidelines reinforce the application of decision-making framework at PHARMAC, based on its factors for consideration (Figure 3), to ensure that all relevant aspects and issues are appropriately considered in the overall decision-making process. Similar to the PBAC framework, PHARMAC's framework helps to incorporate a comprehensive range of factors and considerations when evaluating interventions, ensuring a more comprehensive assessment while maintaining the value neutrality of the analysis.

Figure 3 PHARMAC "Factors for Consideration" in the decision-making process

Source: PHARMAC. Prescription for Pharmacoeconomic Analysis Methods for cost-utility analysis. version 2.2. 2015.
PHARMAC = Pharmaceutical Management Agency (New Zealand).

Germany: Identification and priority of outcomes for the decision-making process

To assess the comparative benefits and harms of a new intervention against the comparator, the IQWiG in Germany considers the effects of an intervention on how a patient feels, functions, or survives [10]. Specifically, the assessment of benefits and harms focuses on the

following patient-relevant outcomes to determine the changes related to disease and treatment: 1) mortality, 2) morbidity (symptoms and complications) and 3) health-related quality of life patient-relevant outcomes. However, the guideline recognises that beneficial and harmful aspects of an intervention can be valued differently for the persons affected. In such a situation it recommends establishing a hierarchy of outcomes to guide the general conclusions on benefit and harm based on the higher-weighted outcomes. Additionally, outcome weighting is also recommended if an overall measure of benefit for comparing interventions is needed (in addition to the disease-specific measures mentioned earlier).

The IQWiG guidelines explicitly state that multi-criteria decision-making procedures or preference determination methods can be employed [10]. Two different approaches are proposed for the conjoint evaluation of benefits and harms: AHP and CA. These approaches:

> 1) weigh the effects on all outcomes, whether qualitative or semi-quantitative, against each other. The goal is to draw a comprehensive conclusion across outcomes regarding the overall benefit or added benefit of the intervention; and
>
> 2) aggregate the various patient-relevant outcomes into a single measure or to reach an overall conclusion by assigning weights to each outcome.

The AHP breaks down a decision problem into criteria and arranges them hierarchically. For example, criteria such as "mortality," "morbidity," and "quality of life" can be used to assess a new intervention [98]. These criteria can then be further subdivided into sub-criteria corresponding to outcomes. Participants (patients or healthcare providers) in the AHP provide binary responses to questions about the criteria, indicating how much one criterion is considered more important than another on a specified scale (thereby establishing the hierarchy). By employing matrix multiplication procedures, weights for the criteria and sub criteria can be determined using a "right eigenvector," ensuring that these weights sum up to 1. The analytic network process is an extension of the AHP that also allows for weighting interdependent criteria [99].

The specific stated preference (CA) technique stipulated in the IQWiG guidelines refers to DCEs. In this case, the results from analysis of the choice task being surveyed, expressed as choice coefficients, are used to derive weights for the attributes by standardising coefficients and exploring the trade-offs made when choosing between a set of products/services.

The IQWiG guidelines do not recommend one specific method (for producing decision weights) over another but specify that the choice between these procedures depends on the specific situation. The AHP is described as suitable for closed-group decision-making, while CA is

considered useful for determining compensation for lost benefit if an intervention is not reimbursed. The guidelines note the importance of considering the number of attributes, cognitive effort required from respondents, and therapeutic indications when selecting the appropriate method to derive decision weights.

The IQWiG has conducted two pilot projects for weighing the outcomes of treatments, applying the AHP for preference analysis in major depression, and a DCE for preference analysis in chronic hepatitis C [100] [101]. Despite being mentioned in the IQWiG guidelines, these methods have not been fully adopted in practice. The guideline emphasises the methodological problems associated with these methods, and therefore, does not recommend their use for routine submissions. However, the guideline does not provide specific details about the situations in which the outlined methods should be utilised. [10] [34].

Conclusion

The examination of HTA guidelines reveals various methods for weighting health outcomes, encompassing both qualitative and quantitative approaches. These methods include MCDA and stated preference techniques like CA and DCE.

The use of these weighting methods varies across jurisdictions and HTA agencies. Some jurisdictions, England and Wales (NICE), the Netherlands (ZIN), Norway (NIPH), Sweden (TLV), explicitly apply QALY weighting or alternative threshold values, while others, Australia (PBAC/MSAC), Canada (CADTH), and New Zealand (PHARMAC), rely on qualitative deliberation without explicit weighting. A common trait among the jurisdictions employing QALY weighting or different thresholds is their consideration of the severity of the health condition for which interventions are under evaluation. Nevertheless, they use varying methods to determine severity, which can result in preferences either favouring younger patients (Absolute Shortfall) or older patients (Proportional Shortfall). This distinction can affect how cost-effectiveness findings are interpreted.

While QALY weighting offers structure, it may oversimplify complex healthcare issues and limit stakeholder input. Qualitative deliberation allows for a more flexible and inclusive approach, considering various factors beyond QALYs, and can incorporate equity, fairness, societal values, and individual preferences into flexible decision-making.

Qualitative methods and those with no fixed thresholds offer greater flexibility, while quantitative methods provide transparency but require robust preference determination. The Australian system is flexible with regards to HTA methods and data requirements an applicant is able to use to make a case for public reimbursement. However, a common criticism with

allowing for flexibility in decision-making is the perceived lack of transparency and comparability in cost-effectiveness, particularly with regards to how data and evidence are used/weighted during the decision-making process. The choice of approach should align with the specific context and objectives of HTA processes.

Why this matters?
In a CEA/CUA, the ICER represents the economic value of an intervention compared with an alternative. The ICER is used as one of the decision-making factors for the consideration of public reimbursement for many jurisdictions, including for Australia. As the health outcomes (e.g., QALYs, LYG) are presented in the denominator of the ICER, methods used to weight outcomes decreases the ICER, resulting in treatment being more cost-effective. A few HTA agencies (NICE, ZIN, and NIPH) allow for the application of modifiers to weight QALYs (proportional shortfall or absolute shortfall) and/or use a higher cost-effectiveness threshold for diseases that are deemed to be 'severe'. These methods reflect a higher willingness-to-pay for the treatment of conditions based on severity, but this has implications for the relative weight of these interventions and populations compared to, for example, preventative treatments. The current approach taken by the PBAC and the MSAC to weighting severity or capacity to benefit is more qualitative in nature. Australia does not have an explicit cost-effectiveness threshold that interventions must meet. Comparative cost-effectiveness is assessed along with less-readily quantifiable factors, including severity and availability of other treatments. This approach permits flexibility in decision-making but may reduce transparency if there is not explicit identification of the weighting of factors.

b. Patient-relevant outcomes including PROMs and PREMs.

Across HTA agencies, health technology claims are made on the effectiveness and safety of new health technologies compared to the alternative treatments. These claims often relate to the patient relevance of the outcomes, as well as clinical importance, and used in the economic evaluations. Determination of what outcomes are relevant to the patients are specified to varying degrees across jurisdictions.

In Australia, patient-relevant health outcomes are defined in PBAC and MSAC guidelines to be those directly related to a patient's quality and/or length of life as impacted by the proposed technology. These outcomes are assessed both in comparative clinical effectiveness and incremental cost-effectiveness, which will be discussed in this section.

Stakeholder input to the Review highlighted the importance of patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) as vehicles for embedding the patient voice within the evidence considered by HTA, facilitating a more patient-centred approach to reimbursement decision-making. While several HTA guidelines reference the use of validated generic and condition-specific PROMs, PREMs are only referred to in one instance (France (HAS) guidelines; PREMs can be provided in supplemental analyses).

The use of PROMs is focused on the assessment of QoL, including via the use of multi-attribute utility instruments (MAUIs) used to derive preference-based measures of QoL (termed utility weights) used for the calculation of QALYs. Results from MAUIs are used to derive utility scores on an interval scale commonly anchored at 0 (death) and 1 (full health). A summary of the MAUIs that are recommended or exemplified for use in HTA guidelines is provided in Table 7.

Table 15 HTA guidelines that recommend or encourage the use of a specific MAUI for CUA

	EQ-5D-5L	EQ-5D-3L	SF-6D	HUI (2 or 3)	QWB	AQoL	CHU9D
Specific MAUI(s) recommended							
England and Wales (NICE)	Yes	Yes					
Scotland (SMC)	Yes	Yes					
New Zealand (PHARMAC)		Yes					
France (HAS)	Yes						
Norway (NoMA/NIPH)	Yes	Yes					
The Netherlands (ZIN)	Yes						
Belgium (KCE)	Yes	Yes					
Spain (CatSalut)	Yes	Yes	Yes				
Japan (C2H)	Yes						
No specific recommendations but examples provided							
Australia (PBAC/MSAC)	Yes	Yes	Yes	Yes		Yes	Yes
Canada (CADTH)	Yes	Yes	Yes	Yes			
Sweden (TLV)	Yes	Yes					
Spain (HTAA)	Yes	Yes	Yes	Yes			
South Korea (HIRA)	Yes	Yes	Yes	Yes			
Singapore (ACE)	Yes	Yes	Yes	Yes		Yes	
Taiwan (CDE)	Yes	Yes		Yes	Yes		

ACE = Agency for Care Effectiveness (Singapore); AQoL = Assessment of Quality of Life; C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CatSalut = Catalan Health Service (Spain); CDE = Centre for Drug Evaluation (Taiwan); CHU9D = Child Health Utility 9D; HAS = French National Authority for Health; HIRA = Health Insurance Review and Assessment Service (South Korea); HTAA = health Technologies Assessment Agencies (Spain); HUI = Health Utilities Index; KCE = Belgian Health Care Knowledge Centre; MAUI = multi-attribute utility instrument; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); QWB = Quality of Well-Being Scale; SF-6D = Short-Form Six-Dimension; SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); ZIN = Zorginstituut Nederland (National Health Care Institute, the Netherlands).

[There was no information pertaining to the choice of MAUIs specified by Luxembourg (MSS)]

Source:

Guidelines: NICE guidelines 2022; SMC guidelines 2022; PHARMAC guidelines 2015; HAS guidelines 2020; NoMA (pharmaceuticals) guidelines 2018; NIPH guidelines 2021; ZIN guidelines 2016; KCE guidelines 2012; CatSalut guidelines 2014; C2H guidelines 2022; PBAC guidelines 2016; MSAC guidelines 2021; CADTH guidelines 2017; TLV report 2022; HTAA guidelines (Lopez-Bastida et al) 2010; HIRA guidelines (Bae et al) 2022; ACE (medical technologies) guidelines 2022; CDE (TasPOR) guidelines 2006

Preferred MAUIs

Ten HTA agencies recommend or require a specific MAUI for the calculation of QALYs. While most of them (England and Wales (NICE), Scotland (SMC), Norway (NoMA/NIPH), Belgium (KCE), Spain (CatSalut)) recommend both the EQ-5D-3L and EQ-5D-5L, three jurisdictions (France (HAS), the Netherlands (ZIN), Japan (C2H)) favour the use of the EQ-5D-5L and only New Zealand (PHARMAC) prefer the EQ-5D-3L. Spain (CatSalut) recommends the use of either the EQ-5D-3L, EQ-5D-5L, or SF-6D. Commonly cited reasons for the choice of recommended MAUI were to improve consistency and comparability across economic evaluations (England and Wales (NICE), Scotland (SMC), France (HAS), Norway (NoMA/NIPH), Belgium (KCE)) and that the MAUI was validated in people of the jurisdiction in which it was to be applied (New Zealand (PHARMAC), France (HAS), Spain (CatSalut)). France prefers the use of the EQ-5D-5L over the EQ-5D-3L due to its improved sensitivity.

Mapping techniques can estimate utility weights from responses of a PROM to a target MAUI, based on previously observed relationships between them. If data of the preferred MAUI is not available, mapping from a PROM to the preferred MAUI is acceptable in most cases, provided the mapping function is well validated (England and Wales (NICE), Scotland (SMC), France (HAS), Norway (NoMA/NIPH), Belgium (KCE), Spain (CatSalut)). Although both the EQ-5D-3L and EQ-5D-5L are recommended by England and Wales (NICE), NICE recommends that the EQ-5D-5L should be mapped onto the EQ-5D-3L to obtain utility weights (as the EQ-5D-5L value set for England published by Devlin et al. (2018) [102] is not recommended for use). This approach is likewise adopted by Norway (NoMA/NIPH). Only Norway (NoMA/NIPH) specifies that mapping from a generic MAUI is preferred over a condition-specific instrument. If there are several mapping functions available, England and Wales (NICE) and France (HAS) recommend their use be tested in sensitivity analyses. In New Zealand (PHARMAC), mapping health states to a MAUI is described as a subjective process, which can involve relating the baseline characteristics or symptoms of patients to health states of the MAUI.

Methods other than the recommended MAUI can be used if evidence showed that it was not appropriate (e.g. in terms of its psychometric properties), or if data were not available. England and Wales (NICE) provides comprehensive guidance on what evidence is acceptable, for example, a comparative study demonstrating superiority of an alternative measure over the EQ-5D in terms of content validity, construct validity, reliability and/or responsiveness can establish support for the chosen measure [103] It is nonetheless preferred in England and Wales (NICE) and the Netherlands (ZIN) to present the EQ-5D alongside other alternatives even if it is not appropriate.

The remaining ten HTA agencies (Australia (PBAC/MSAC); Canada (CADTH/INESSS), Germany (IQWiG), Sweden (TLV), Spain (HTAA), South Korea (HIRA); Singapore (ACE); Taiwan (CDE)) do not recommend a specific MAUI to calculate QALYs but provided examples. Two agencies (Canada (INESSS); Germany (IQWiG)) do not provide any examples of MAUIs despite discussing the use of cost-utility analyses in the guidelines. Some reasons cited by South Korea (HIRA) and Germany (IQWiG) guidelines for not recommending a specific MAUI are the lack of comparative evidence on their performance, discrepancies across value sets for different MAUIs, and no definitive advantage of any MAUI. Instead, examples of MAUIs are provided by some jurisdictions, including the EQ-5D, HUI-2, HUI-3, SF-6D, AQoL and CHU-9D. In the PBAC and MSAC guidelines, the usage of MAUIs other than these measures requires a detailed discussion of the domains, scoring, validity, reliability, responsiveness and MCID. Likewise, the demonstration of good psychometric properties of the selected MAUI is required in several jurisdictions (England and Wales (NICE), Canada (CADTH), Germany (IQWiG), the Netherlands (ZIN), South Korea (HIRA)) and Singapore (ACE). Other considerations are that the selected MAUI should be validated in the country to which it will be applied (Australia (MSAC), Germany (IQWiG), Taiwan (CDE)), validated in the health condition and intervention (Australia (MSAC)), and should reflect the health states of interest (Canada (CADTH), Germany (IQWiG)).

Most guidelines explicitly state that patients should complete the MAUI. However, if patients are unable to complete the measure, some guidelines (England and Wales (NICE), France (HAS), Japan (C2H) prefer carers or relatives over healthcare professionals to serve as a proxy, while others (Belgium (KCE), Spain (CatSalut)) do not state a preference for proxy. No guideline references the use of MAUIs specifically developed or adapted for proxy use.

Population- and Condition-specific MAUIs

Five HTA agencies (Australia (PBAC/MSAC), England and Wales (NICE), France (HAS) and Belgium (KCE)) refer to the use of paediatric-specific MAUIs. PBAC and MSAC guidelines list the CHU9D as an acceptable measure, while Belgium (KCE) recommends the use of the EQ-5D-Y. England and Wales (NICE), and France (HAS) acknowledge the need to consider alternative measures in children and adolescents but do not recommend a specific MAUI. Instead, potential instruments were listed, which included the HUI2, HUI3, CHU9D, AQoL-6D and EQ-5D-Y, noting that UK value sets were only available for the CHU9D and HUI2 [104], and a French value set was only available for the HUI3. The Office of Health Economics raised the issue of the use of QALYs as a measurement of outcome in CUA, in the context of whether child QALYs is equivalent to adult QALYs [105]. There is currently work funded by the Medical Research Futures Fund (MRFF) underway in Australia to investigate how child QALYs are valued, namely,

within the QUOKKA (Quality of Life in Kids: Key Evidence in Australia) research program [106, 107].

The use of condition-specific MAUIs is specified to only be used when a preferred or generic MAUI is not appropriate in terms of psychometric properties in England and Wales (NICE) and Canada (CADTH) guidelines. The Netherlands (ZIN) guidelines state that even if the EQ-5D-5L is expected to not be sensitive, it should still be administered alongside other PROMs. Likewise, condition-specific instruments are viewed as a complement or supplementary to generic MAUIs in France (HAS), Norway (NoMA/NIPH), Belgium (KCE) and Singapore (ACE) guidelines. Only France (HAS) explicitly does not recommend the use of a condition-specific instrument to generate utilities, due to variations in its validity and lack of French value sets, but accepted its use in sensitivity analyses.

Mapping from a condition-specific instrument to generic MAUI using a validated mapping function is generally acceptable but is discouraged in Germany (IQWiG) and Canada (CADTH). Instead, CADTH requires the condition-specific instrument to be able to directly provide utilities. The consideration of whether domestic value sets were incorporated in the mapping functions is only stated in Australia (PBAC/MSAC) guidelines), although France (HAS) mentioned a lack of domestic mapping functions.

Utilities from clinical events

The adjustment of utilities by applying a disutility for an adverse event (AE) is an explicit approach addressed in the HTA guidelines of Australia (MSAC), England and Wales (NICE), Canada (CADTH), and France (HAS). MSAC specifically recommends the use of the multiplicative method over additive or minimum methods to account for impact on HRQoL of concurrent clinical events. England and Wales (NICE) guidelines requests justification for the selection of disutilities for AEs known to affect quality of life [108]. The source for disutilities is only stated in France's (HAS) guidelines, as either estimated from the primary trial or obtained from a systematic literature review.

Preferred value sets

To calculate utility weights from MAUIs, most HTA agencies state that value sets obtained from the general population are recommended. Norway's (NoMA/NIPH) guidelines additionally state that the use of an experience-based value set (i.e., of individuals who have experienced impaired health states) may be used, provided this is justified and variation from the population-based value set is explained. Australia (PBAC), England and Wales (NICE), and Canada (CADTH) explicitly state that value sets are to be determined by choice methods such as

time-trade off (TTO) or standard gamble (SG). In general, value sets should be country-specific, except for Norway (NoMA/NIPH) and Singapore (ACE), which recommended the use of the UK value set. Some jurisdictions require the use of specifically cited sources that provide the value sets (England and Wales (NICE), Canada (CADTH), France (HAS), the Netherlands (ZIN), Singapore (ACE)), while this was preferred or recommended in others (Australia (PBAC), New Zealand (PHARMAC), Norway (NoMA and NIPH), Belgium (KCE), Spain (CatSalut, HTAA), Japan (C2H0, Taiwan (CDE)). South Korea (HIRA) did not recommend any, citing discrepancies in the EQ-5D-3L and -5L South Korean value sets. If a domestic value set is not available for the selected MAUI, the use of a foreign value set is acceptable in France (HAS; for paediatric MAUIs), Belgium (KCE) and South Korea (HIRA). If a domestic general population value set is not used, sensitivity analyses or justifications for using alternative value sets are recommended for Australia (PBAC/MSAC) and New Zealand (PHARMAC).

Scenario-based methods

Scenario-based methods use vignettes which describe health states for a hypothetical patient that are then valued in a preference elicitation task, commonly by the general population, to obtain utility weights. These methods include TTO, SG, DCEs, and visual analogue scales. Sweden (TLV) is the only HTA agency that prefers scenario-based utility valuation (specifically, TTO or SG) over the use of MAUIs to obtain QALYs. Conversely, most HTA agencies (Australia (PBAC/MSAC), England and Wales (NICE), Canada (CADTH), New Zealand (PHARMAC), the Netherlands (ZIN), Belgium (KCE), Spain (CatSalut), Japan (C2H), South Korea (HIRA)), and Singapore (ACE) prefer the use of MAUIs as the source of utility values. Reasons cited for not preferring scenario-based methods are that these methods are complex and difficult to design and implement, reduce comparability across evaluations, and the resulting utility weights are highly dependent on the validity of the described health states (Canada (CADTH), Spain (CatSalut), South Korea (HIRA)). Only France (HAS) does not accept the use of scenario-based methods in base case analyses.

Scenario-based methods are described as usually being completed by the general population (Australia (PBAC/MSAC), Canada (CADTH), Japan (C2H)), patients (France (HAS), Sweden (TLV)), both the general population and patients (England and Wales (NICE), Spain (CatSalut)), or clinical experts (England and Wales (NICE)). Among the methods, choice-based methods (including TTO and SG) are preferred over rating scales by Spain (CatSalut) due to greater consistency and less potential for scaling bias.

Sources of utilities

Recommended sources of utilities are specified in a standalone section in most guidelines. Utilities directly measured in clinical trials are mainly preferred as the source for utilities, but these can also be sourced from relevant clinical trials identified in systematic literature reviews. However, the use observational studies to obtain utilities is also acceptable in Scotland (SMC) and France (HAS). Population matching studies are only referenced by PBAC and MSAC, which also provides considerations for mitigating potential biases.

The inclusion of published research to obtain utilities should be justified (Australia (PBAC/MSAC), England and Wales (NICE), Canada (CADTH), Singapore (ACE). CADTH further detailed that the rationale for inclusion should be based on fitness for purpose, credibility, and consistency. If there is more than one acceptable source of utilities, sensitivity analyses are to be reported (Australia (PBAC/MSAC), England and Wales (NICE), Canada (CADTH), France (HAS), Norway (NoMA/NIPH). Singapore (ACE)). The use of foreign studies is noted as acceptable only if domestic data is unavailable in France (HAS), Belgium (KCE) or Japan (C2H). Only New Zealand (PHARMAC) recommends the use of a database with disability weights, citing the Global Burden of Disease Study to check the consistency and face validity of EQ-5D utility weights.

Conclusion

There is largely consensus among HTA agencies in terms of the choice of MAUI, with the EQ-5D, HUI and SF-6D cited in most guidelines. Notably, agencies that take a more prescriptive approach provide extensive guidance on alternative methods when the recommended MAUI is deemed inappropriate or unavailable. While there remains ongoing debate about the advantages and disadvantages of recommending a single type of MAUI [29, 30], other agencies make up for limitations of a broader approach by emphasising the need for over well-justified choices accompanied with sensitivity analyses.

Why this matters?
Australian PBAC and MSAC guidelines provide key considerations on a range of methodological aspects regarding MAUI selection, use of value sets and sources of utilities, with no substantial deviation from other guidelines. Most jurisdictions, including Australia use MAUIs to obtain utility weights for cost-utility analysis. Multiple psychometric comparisons across MAUIs suggest that no single instrument is superior across all health conditions and interventions [109, 110]. There is increasing acknowledgement among jurisdictions that population-specific and condition-specific MAUIs, may in certain instances be appropriate to be more informative utilities than generic MAUIs.

Methods such as mapping from condition-specific instruments to generic MAUI, and the use of scenario-based methods have continued to develop, affording greater flexibility in deriving utilities.

In light of the proliferation of various PREMs, condition-specific MAUIs, mapping techniques, and MAUIs derived from profile instruments, there is value in maintaining flexibility in methods to obtain utilities across a variety of contexts.

c. Consideration of patient preferences

Patient preferences are defined as the incorporation of views and experiences of people living with a condition and/or their representatives [111], over and above the measurement of preferences for health outcomes as incorporated into QALYs (see the previous section). There are two main methods for incorporating patient preferences, through patient participation or through inclusion of patient-based evidence [31-33].

- Participation: patient preference input refers to the inclusion of patients and/or their representatives in discussions at different stages of the HTA process e.g. committee meetings, calls for written comments, inclusion of patient representatives on advisory groups, testimonials, focus groups, organisation of a patient panel. An important distinction between participation and patient based evidence is that participation does not need a specific methodology. Peer review or critical assessment of the quality of any methods used is not an important factor when including patients through participation [33].
- Patient-based evidence: patient preference input refers to the collection of patients'/patient representatives' values and experiences. This includes studies collecting data using a systematic method (e.g., survey, qualitative interviews), where data is analysed quantitatively. For example, data collected from patients for valuation of health states to be used in the calculation of QALY weights (e.g., via TTO); or stated preference methods such as a discrete choice experiment (DCE) could be used to examine patient preferences and presented as supporting evidence.

A summary of whether patient preference was considered either through participation or use of patient-based evidence by jurisdiction is provided in Table 16. In general, many jurisdictions consider patient preferences through direct participation. This includes Australia (PBAC/MSAC), England and Wales (NICE), Scotland (SMC), Canada (CADTH), New Zealand (PHARMAC), Germany (IQWiG), Singapore (ACE), and Norway (NIPH). There were also a few jurisdictions that

explicitly mention consideration of patient-based evidence methods, such as England and Wales (NICE), Germany (IQWiG), Sweden (TLV), The Netherlands (ZIN) and Japan (C2H), France (HAS), Norway (NIPH), and Singapore (ACE). Patient preferences, captured either through means of participation or patient-based evidence, are often used as supporting evidence separate from economic modelling or QALYs. However, there have also been challenges raised about incorporating direct input including tight timeframes [31, 34, 35], additional burden placed on patients [31, 35], information mismatch between patient groups [35], and uncertainty of whether a treatment has met safety standards.

For Japan (C2H), Germany (IQWiG) and Sweden (TLV), when QALYs are used as the outcome measure, patient valuation of health states in the calculation of QALY weights were preferred or accepted. This would require a quantitative preference study to elicit these values, hence a 'yes' has been put for 'quantitative studies'. In Germany (IQWiG) and The Netherlands (ZIN), quantitative preference studies are also accepted for reasons other than QALY estimation (see country summaries below).

Table 16 Explicit inclusion of patient preference evidence by jurisdiction

Jurisdiction (agency)	Participation	Patient-based evidence via:		Input used:	
		qualitative studies	quantitative studies	As supporting evidence?	In assessment of costs and benefits?
Australia (PBAC/MSAC)	yes			yes	
England and Wales (NICE)	yes	yes	yes	yes	
Scotland (SMC)	Yes				
Canada (CADTH)	Yes			yes	
New Zealand (PHARMAC)	yes			yes	
France (HAS)			yes	yes	
Germany (IQWiG)	yes		yes	yes	yes
Norway (NIPH)	yes	yes		yes	
Sweden (TLV)			yes		yes
The Netherlands (ZIN)			yes		yes
Belgium (KCE)	yes				
Japan (C2H)			yes		yes
South Korea (HIRA)	yes			yes	
Singapore (ACE)	yes			yes	

ACE = Agency for Care Effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; HAS = French National Authority for Health; HTA = Health Technology Assessment; KCE = Belgian Health Care Knowledge Centre (Belgium); IQWiG = Institute for Quality and Efficiency in Health Care; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); SMC = Scottish Medicines Consortium; NIHTA = Taiwan Society for Pharmacoeconomics and Outcome Research; TLV = Dental and

Pharmaceutical Benefits Agency (Sweden); ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).
Agencies not explicitly stating use of patient preferences through participation or patient-based evidence include:; Spain (various); Luxembourg; Taiwan (NIHTA).
Source: PBAC guidelines 2016; MSAC guidelines 2021; NICE guidelines 2022; SMC guidelines 2022; CADTH guidelines 2017; PHARMAC guidelines 2015; IQWiG guidelines 2022; TLV (Continued study on evaluation methods and payment models for new medicines) guidelines 2022; ZIN (Guideline for the Conduct of Economic Evaluations in Health Care) guidelines 2016; KCE guidelines 2012; C2H (Guideline for preparing cost-effectiveness evaluation to the central social insurance medical council) guidelines 2022; HAS guidelines 2020; NoMA (Guidelines on how to conduct pharmacoeconomic analyses) guidelines 2012; NoMA (medical devices and diagnostic interventions) guidelines 2021; ACE (Drug evaluation methods and process guide) guidelines 2023; HIRA guidelines (Bae et al) 2011.

Findings from relevant organisations

A number of not for profit, patient and industry organisation websites were searched for relevant information on patient preferences. Medicines Australia supports a patient centred approach and argues for the cost benefit of medicines to be considered from a patient perspective throughout the reimbursement process [112]. Rare Cancers Australia likewise advocates for patient involvement at all stages of HTA, and extends the perspective to other stakeholders impacted by disease and treatment (e.g. impacts on a person's family, employer, and employers of partners) [113]. Rare Cancers Australia also place importance on capturing patients' lived experiences and that there is diversity in this representation [114]. On the EUnetHTA website, the preferred method for capturing patient preferences is through participation including open calls to patient organisations as well as one on one conversations, group discussion and scoping e-meetings with patients.

Findings from the literature

van Overbeeke, Forrester [115] conducted focus groups with HTA representatives from Canada (CADTH), Germany (IQWiG) and Belgium (KCE) to explore how patient preferences could be incorporated into HTA processes in their respective jurisdictions. Canada and Belgium have processes in place for direct participation from patients e.g., open calls for input, invitation of patient representatives to discuss clinical trial research questions and outcomes. HTA representatives in Belgium and Germany raised that tight timeframes can make integration of patient preferences challenging. Across all three jurisdictions there was interest to use patient preference information for scientific advice and value assessments. However, patient preferences should be included as supporting evidence, separate to QALYs or MCDA according to those agencies. Canada and Belgium see a role for patient preference information in providing early scientific advice alongside clinical evidence. Patient preference studies i.e., indirect input, should be included as a separate section of the assessment report or discussion. The HTA representatives interviewed in van Overbeeke, Forrester [115] would be interested in patient preference studies that investigate the following attributes: benefits, risk,

administration route/schedule, travel burden, out of pocket costs, manageability in daily life and user friendliness.

Two publications (Elvsaas, Ettinger [35], Gunn, Regeer [116]) reviewed patient involvement, i.e. , participation, in HTA processes in Europe. Gunn, Regeer [116] interviewed relevant HTA personnel in Ireland, the Netherlands, Norway and Scotland and presents three case studies of how patient knowledge was used in various stage of HTA processes. Through these three case studies, Gunn, Regeer [116] demonstrated how direct participation can be used to reframe and highlight important points at different stages of the HTA process from the patient perspective. This includes the patient perspective of what is being assessed, what the technology consists of, its effects and its acceptability. Elvsaas, Ettinger [35] collected the experiences of EUnetHTA project managers with obtaining and using patient preferences in the form of direct input. There was more successful patient involvement in the assessment of pharmaceutical technologies (12/14)[4] as opposed to other technologies (11/22)[4]. Although in the case of other technologies, patient input was not sought for 7/22[4] assessments. It was found that patients and patient organisations was most associated with the European Medicines Agency and the HTA Network Stakeholder Pool. An online patient input template was often used by EUnetHTA project managers in the early phase of the assessment process before using other approaches e.g. one on one conversations. Although it was found that identifying individual patients for one on one conversations can be challenging due to tight timelines, burden of disease on patients and the need to include a specific population group. Information from patient input was primarily used to inform outcomes, grading of recommendations, in discussions or as a supplement to information in literature.

Gagnon, Tantchou Dipankui [117] provides a review of patient participation into HTA processes by patients and public from 2009 to 2019. Thirty-one studies were identified covering Canada, Australia, England, Germany and Finland. Direct participation by patients and the public were used to advise on a topic under study e.g., draft of HTA recommendations, framework or test and also at different stages of the HTA process e.g., 'at the same table' with other stakeholders in working group, receive information about a HTA being conducted.

Mason, Searle [118] goes a step further and examines how the impact of participation from patients in HTA has been evaluated. Six studies were included in this review. It was found that evaluation of patient involvement in HTA was mainly through reviews of HTA reports, some through qualitative interviews and a few through quantitative analysis. In terms of impact,

[4] Numbers are reported from Elvaas et al (2021): number of papers that mentioned item/total number of papers in the literature review.

patient involvement was found to be helpful in increasing the reviewers' understanding of the technology. The two studies that conducted quantitative analysis found no significant association between the presence versus absence of patient involvement and positive funding recommendation. A finding of note was that patient groups question whether their contributions were meaningful.

Marsh, de Bekker-Grob [119] presents a critical review and provides some recommendations of how quantitative patient preference studies could potentially be used to inform different stages of the HTA process. Six different use cases are identified; trade-off assessment, preference share, estimation of QALY gains, construction of efficiency frontiers and in MCDA. The researchers highlight that quantitative patient preference data can be used to understand how patients trade-off between differences in available technologies or to understand the relative importance of (HTA relevant) endpoints. They could also be used to predict uptake of treatment, which can be used in cost effectiveness or budget impact analyses.

One paper covered both input of patient preferences through participation and patient-based evidence methods. Chachoua et al [31] reviewed the use and integration of patient preferences up until May 2019. In terms of initiatives to integrate patient preferences in decision-making, 20 studies were noticed, mostly in Europe (n=8) or a European country (n=5) followed by the US (n=6). These initiatives were largely qualitative. Germany was the only country to explore the incorporation of quantitative patient preference studies in the HTA decision-making process, however this was not a recommended approach in Germany. Chachoua et al [31] also identified studies where attempts were made to incorporate patient preferences; twenty-five patient preference elicitation studies were found. Fifteen informed benefit risk assessment, 10 HTAs and 6 informed pricing/reimbursement decision-making. There were various attributes assessed including those related to efficacy and safety (n=24), treatment conveniences e.g., mode and frequency of admin (n = 14), preferences for treatment cost (n=8), HRQoL (n= 7). Disease areas of interest included: metabolic disorders e.g. diabetes, obesity (n=6), rare diseases (n= 4), oncology (n = 6), infectious diseases (n=3) and other diseases (n=6). In terms of elicitation method, the majority of studies used a DCE (n=18), there was also use of Best Worst Scaling combined with a DCE (n=4), visual analog scales (n=1), rating scales (n=1), standard gamble (n=1) and one qualitative study.

Huls et al [120] provides a review of patient preferences from 2013-2017 and discusses some of the challenges faced in integrating them into HTA. 67 articles were included in the review covering Canada, the UK, Germany, US, Australia and the Netherlands. A major challenge identified in, (29/67 or 43%) of studies reviewed, was choosing the method for eliciting

preferences. How the quality of patient preference studies should be assessed (17/67 or 25%), at what stage should preferences inform decision-making (16/67 or 24%), how should preference studies be evaluated in comparison/addition to clinical and economic evaluation studies (15/67 or 22%) were also some key questions identified when thinking about how to integrate patient preferences into HTA processes.

Dimitrova et al [32] explored barriers to incorporating patient preferences in HTA, specifically in the Central and Eastern European countries (CEE). From a scoping review (2010-2020) and workshop with CEE stakeholders 25 potential barriers were identified and categorised. Barriers could be grouped into barriers from a payer/HTA body perspective and a patient perspective. Payer/HTA body barrier include limited willingness to involve patients, conflict of interest/confidentiality, difficulties to finding the 'right' patient representative, lack of human resources at relevant public institutes and not knowing how to involve patients. Patient barriers include lack of understanding the decision context, lack of knowledge and guidance of evidence-based advocacy, lack of resources to be spent on meaningful patient representation and lack of ethical guidance for representativeness.

Conclusion

From reviewing country HTA guidelines, HTA websites and the literature, inclusion of the input of patient preferences though participation in the HTA process is a well-established method. What is less established is the use of patient-based evidence requiring quantitative collection of patient preference information. There are a few jurisdictions that consider the formation and use of such evidence in their HTA guidelines, namely, Germany, Japan, Sweden and the Netherlands. By far, the most accepting country of quantitative preference studies has been Germany, who have investigated the use of quantitative methods like CA and AHP to capture patient preferences. However, methodological issues have prevented its routine use in German HTA decision-making. This is supported by findings from the literature that there are many questions that need to be answered before patient preference studies can be integrated into HTA processes. This includes questions like choice of method for gathering preferences, quality assessment of preference studies and their weighting in decision-making.

Australia is similar to many of the jurisdictions reviewed in that participation is accepted as a means of capturing patient preferences. Indeed, consultation with patients and their representatives is very well established in Australia with processes in place for PBAC and MSAC.

Why this matters?

The main method used in the HTA to include patient preferences is through participation. In Australia, the current HTA process does allow for participation, where the public (including patients, carers, consumer groups and health professionals) can provide direct input on applications before PBAC or MSAC consideration, and this forms part of the evidence considered by the Committees. Both the PBAC and MSAC also have consumer representatives within their membership.

However, there are concerns that this involvement does not have a meaningful impact, and the interests of the affected patient population and their carers/families are not reflected in the decision-making process. Noting these concerns in the current HTA process, findings from the literature describe difficulties that are associated with an increased rate of participation are due to tight timeframes.

d. Indirect and non-health benefits and harms

Indirect and non-health benefits/harms refer to any benefits/harms that are not related to direct health and healthcare consumption of the patient. Examples of indirect and non-health benefits discussed on HTA websites, and the literature includes outcomes relating to productivity gains/losses; when impacts accrue to family members or caregivers of the patients; better educational outcomes occurring due to improvements in school attendance.

The outcomes and approaches used in economic evaluation across the jurisdictions and described in the literature include:

- Presenting a societal perspective in economic evaluation, using willingness to pay (WTP) approach to valuation, and/or including productivity costs.
    - Application of WTP is more common outside the health care sector and is an important input for valuation in CBA. WTP reflects the maximum amount of money an individual is willing to pay for a 'commodity', which is an indicator of utility or satisfaction. In the context of health, the WTP approach has been used to ascertain the value that people attach to health care outcomes. There are ethical issues pertaining to using WTP where the valuation of health relies on an individual's ability to pay and income; measurement of health gains using WTP is considered to favour a wealthier populations [121]. Methods to elicit WTP discussed in HTA guidelines refer to contingent valuation and DCE.
    - The main methods used to estimate the value of productivity changes in an economic evaluation are: 1) the human capital approach; and 2) the friction

cost approach [122, 123]. A third approach is also discussed in the literature, the US Panel Approach, recommended by the US Panel on Cost-Effectiveness in Health and Medicine) [124].

- Inclusion of caregiver or family QALYs in economic evaluations (Scotland, SMC; Norway, NoMA).
- Inclusion of patient and caregiver's time and costs for duration of treatment administration and/or travel time in economic evaluations (Canada, CADTH; Belgium, KCE; Singapore, ACE; The Netherland, ZIN; Norway, NoMA).
- Inclusion of intersectoral costs and benefits. For example, impacts related to discontinuing education and judicial involvement, which may be relevant for preventive interventions (Canada, CADTH; The Netherlands, ZIN; South Korea, HIRA). Methods described to consider trade-off between health and intersectoral costs and benefits include stated preference methods such as TTO and SG (Canada, CADTH).
- Value of knowing: incorporates any impact on the well-being of a patient beyond the changes in health outcomes that can be attributed to changes in healthcare provided (the health benefits associated with a medical services). Testing for heritable conditions may cause additional stress if there is an ambiguous result rather than if there is a positive result. There may also be guilt for passing on heritable diseases, or survivor guilt for unaffected siblings (Australia, MSAC). This indirect health outcome is applied to the assessment of diagnostic technologies for which there is some component of 'knowing' associated with the outcome of the intervention.

Comparisons of HTA processes across jurisdictions

The methods and processes used to measure indirect and non-health benefits and harms discussed in the HTA guidelines and websites of the jurisdictions of interest are presented in Table 17. The subsequent sections provide detailed explanations of the methods and processes employed by relevant agencies, elaborating on their respective approaches.

Table 17 Indirect and non-health benefits and harms methods by jurisdiction

Jurisdiction	Mentioned in the guideline	Methods and evaluation approaches	Application
Australia (PBAC, MSAC)	Yes.	FCA CCA (MSAC) CBA (PBAC) CA or a DCE Impact on carers QoL Value of knowing (MSAC only)	Do not include in the base-case evaluation; Presented as supplementary analyses and outcomes.

Jurisdiction	Mentioned in the guideline	Methods and evaluation approaches	Application
England and Wales (NICE)	Yes.	Method not specified.	Productivity costs should not be included in the reference case. Non health benefits: If substantial proportion of the benefits are associated with significant benefits other than health and only after agreed upon with the Department of Health and Social Care.
Scotland (SMC)	Yes.	CCA (only for ultra-orphan medicines) Impact on carers QoL (measured using tools such as Carer Experience Scale). Assessment of impact on NHS staffing, infrastructure, and training requirements.	Presented as supplementary analyses and outcomes. Considers impact beyond direct health benefits and on specialist services.
Canada (CADTH)	Yes.	CCA CBA Non-health effects using time-trade-off or standard gamble. FCA patient and caregiver time for paid labour, and opportunity cost method to estimate productivity costs related to unpaid labour. FCA for productivity losses.	Presented as supplementary analyses and outcomes. Non-health effects considered if the decision problem requires a perspective other than that of the publicly funded health care payer in a non-reference case analysis.
New Zealand (PHARMAC)	Yes.	Not specified (reasons are given for exclusion of indirect benefits). If indirect health benefits are considered, they should be estimated and discussed in the report as a scenario analysis.	Recommended indirect costs are not included in CUAs. If the treatment might have a measurable but indirect impact on the HR-QoL of others, such as family and caregivers
France (HAS)	Yes.	HCA or FCA	Health effects are prioritised. Non-health outcomes are not given equal emphasis but can be presented as supplemental analysis
Germany (IQWiG)	Yes.	FCA HCA	Productivity losses using the FCA with HCA in sensitivity analyses. If the time expenditure of affected persons or relatives is considered, the net wage is used as method to estimate it.
Norway (NoMA, NIPH)	Yes.	Value of time for caregivers and patients Carer HRQoL quantified in QALYs.	Productivity changes must not be included. If the intervention and the comparator have different time requirements. The costs of the intervention and the comparator must be presented in a way that reflects the differences in time use.
Sweden (TLV)	Yes.	Including caregivers QoL standardised approximation – a standard rate.	Societal perspective is used for reference case. Only when the impact on family members is high for the condition and the treatment can lead to an improvement in health-related quality of life for the family members.
Belgium (KCE)	Yes	HCA. FCA	Include in supplemental analysis if productivity losses, non-health care

Jurisdiction	Mentioned in the guideline	Methods and evaluation approaches	Application
		Incremental number of unpaid working days Caregivers QoL	costs and/or unrelated health care costs are deemed important for a specific treatment.
The Netherlands (ZIN)	Yes.	Reference case includes societal perspective including productivity using FCA and costs for patients and families. Intersectoral costs and benefits[a]. Well-being via ICECAP (only for long-term care interventions)	FCA is presented for the reference case using a societal perspective. Intersectoral costs and benefits included for preventive interventions.
Spain (HTAA)	Yes	Not specified.	Include cost of labour production losses or lost time. Include cost of caregiver in evaluation when the perspective used requires.
Japan (C2H)	Yes	HCA Impact on carer's QoL (no method specified)	Included in supplemental analysis only if this can be estimated using Japanese data.
Taiwan (TaSPOR/CDE)	Yes	HCA	Societal perspective is used for reference case.
Singapore (ACE)	Yes.	No specific methods identified in guidelines. Non-health outcome relevant to the patient, or indirect impact on the quality of life of caregivers (e.g., family of the patient) will be considered on a case-by-case basis at the discretion of ACE's committees.	Included in supplementary analysis if important societal implications are involved (e.g., economic productivity impact).

ACE= Agency for Care Effectiveness; CBA= cost benefit analysis; CCA= cost consequence analysis; CUA= cost-utility analysis; FCA = friction cost approach; HAS = French National Authority for Health; HCA – human capital approach; HRQoL= Health related quality of life ; IQWiG = Institute for Quality and Efficiency in Health Care (Germany); MSAC= Medical and Scientific Advisory Council; NHS= National Health Service; NICE= National Institute for Health and Care Excellence; NIPH = Norwegian Institute of Public Health; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; QoL = quality of life; SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; UK= United Kingdom; ZIN= The National Health Care Institute;
a The document 'Handleiding intersectorale kosten en baten van (preventieve) interventies' published in 2014 by Maastricht University, is referenced for methods, however, the document is not in English and was not possible to retrieve from the source.
Source: ACE guidelines 2023; C2H guidelines 2022; CADTH guidelines 2017; CDE (TasPOR) guidelines 2006; HAS guidelines 2020; HIRA guidelines (Bae et al) 2022; HTAA guidelines (Lopez-Bastida et al) 2010; INESSS guidelines 2022 [36]; IQWiG guidelines 2022; KCE guidelines 2012; MSAC guidelines 2021; NICE guidelines 2022; NoMA guidelines 2018; PBAC guidelines 2016; PHARMAC guidelines 2022; SMC guidelines 2022; TLV guidelines for precision medicine 2022 [37]; ZIN guidelines 2016.

Three jurisdictions (the Netherlands (ZIN); Taiwan (CDE); Sweden (TLV)) states the societal perspective is used in economic evaluation for the reference case. For all other agencies, the healthcare payer perspective is considered for the reference case (including for Australia). This differentiation in perspective results in different methods being considered particularly relating to inclusion of indirect and non-health costs and benefits in modelling, where it is recommended that inclusion of indirect and non-health benefits be presented as supplementary analyses or outcomes across the jurisdictions/agencies.

Five agencies recommended that indirect or non-health benefits or harms be included in supplementary analyses (Australia (PBAC); England and Wales (NICE); Canada (CADTH); Singapore (ACE); France (HAS)). By consigning non-health benefits to supplementary analysis, there is a potential lack of transparency regarding the extent to which they might impact the

decision-making process. The HTA process in Australia is flexible in providing guidance on inclusion of indirect and non-health benefits as well as other factors, albeit as recommendations to presented as supplementary analyses (PBAC, MSAC). England and Wales (NICE) state that non-health benefits be considered only after obtaining explicit agreement with the Department of Health and Social Care (NICE; Published: 31 January 2022).

As mentioned by New Zealand (PHARMAC), HTA is a deliberative process informed by quantitative decision frameworks, but those frameworks are not deterministic. Decision makers can choose how much and how to weight quantitative and qualitative results to arrive at a decision. Therefore, submissions should provide as much information as possible regarding indirect and non-health benefits, while the deliberative process of HTA should be sufficiently flexible to consider these benefits [7]. In contrast, PHARMAC recommends that indirect costs such as productivity effects not be included, listing reasons of double-counting of impacts, difficulty in accurate quantification and lack of validity in assumptions (e.g., zero rate of unemployment), differentiation in earning levels biasing against individuals not in paid labour. PHARMAC recommend that indirect patient costs be incorporated in QALY estimates through the utility values. In PHARMAC's view, inclusion of societal costs is beyond the remit of PHARMAC's considerations (PFPA Guidelines v2.2, 2015, pp48-49).

Productivity

The two main methods discussed in the HTA guidelines used to estimate the value of lost productivity are: 1) the human capital approach; and 2) the friction cost method [122, 123]. These two methods can yield divergent estimates due to the differences in the key assumptions [125].

Among those jurisdictions that specified the methods to use to value productivity losses (Australia (PBAC, MSAC); Canada (CADTH); Germany (IQWiG); Belgium (KCE); The Netherlands (ZIN); Japan (C2H); Taiwan (TaSPOR/CDE); France (HAS)), only Belgium (RIZIV–INAMI) and Germany (IQWiG) reference the human capital approach. For Germany (IQWiG) this should be as part of a sensitivity analysis, whereas Belgium (RIZIV–INAMI) suggest its use to value short-term lost productivity during paid work. Australia (PBAC and MSAC); Canada (CADTH) and Netherland (ZIN) specify a preference in the HTA guidelines for the friction cost approach over the human capital approach when presenting results from these analyses; noting productivity costs are included in the reference case only in the Netherlands (ZIN).

The human capital approach assumes accrual of losses over a person's lifetime, where the productivity of an individual is measured by the discounted stream of future earnings [126].

However, the human capital approach has been criticised for grossly overstating productivity losses as it implicitly assumes that the labour market clears (i.e., is in equilibrium, so there is never 'unemployment'). Secondly, the human capital approach assumes those who die prematurely due to illness would have worked until the end of their working life [122]. The problems with the human capital approach led to the development of the friction cost approach, which assumes that productivity losses are only incurred during the time taken to replace an employee, known as the friction period [123, 127]. The friction period represents production loss due to reduced labour and is a standard time period defined as the time from when a vacancy occurs to when an individual fully replaces the person who is absent due to illness in the position [128].

Another approach described in the literature is the US Panel Approach, recommended by the US Panel on Cost-Effectiveness in Health and Medicine [124]. The US Panel Approach values productivity costs in terms of quality of life effects and assumes that income changes due to health. This method implicitly assumes that there is a stable relationship between productivity, income and quality of life. The Panel considered that explicitly including productivity costs would lead to double counting because (QoL) valuation is included in the health effects [124, 129].

HTA agency guidelines vary in their recommendations regarding the inclusion of productivity losses in economic evaluations. For instance, Germany [130] only consider absenteeism from paid work, whereas, the Netherlands [131] encourage inclusion of absenteeism and presenteeism, and France [132] encourages inclusion of unpaid work loss. The NICE guidelines (England and Wales) [133] explicitly state that productivity costs are not included in the reference (i.e., base) case. The PBAC and MSAC guidelines [134] stipulate a broader social perspective beyond the patient and health care system can be presented in a supplementary analysis in addition to the base case, where productivity costs are not included.

Impact on caregiver's quality of life

Ten agencies refer to presentation of the impact of an intervention on caregivers' QoL (Australia (PBAC); England and Wales (NICE); Sweden (TLV), Scotland (SMC); Canada (CADTH); New Zealand (PHARMAC); Singapore (ACE); Norway (NoMA); Belgium (KCE), Japan (C2H)). The PBAC guidelines specify that claims pertaining to non-health outcomes in people other than patients receiving treatment are presented in supplementary analyses. Internationally, other agencies uniformly emphasise the inclusion of caregivers' QoL solely within specific contexts:

- England and Wales, NICE: all health effects for patients, and, when relevant, carers should be considered. NICE specify that when presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's HRQoL and how the technology affects carers.
- Sweden, TLV: for advanced therapy medicinal products [37]
- Scotland, SMC: for ultra-orphan drugs [4]
- Canada, CADTH: in non-reference case analyses as it would fall outside the perspective of the publicly funded health care payer [135].
- New Zealand, PHARMAC: should be estimated and discussed in the (submission) report as a scenario analysis[7].
- Singapore, ACE: considered on a case-by-case basis at the discretion of ACE committees in a supplementary analysis [136].
- Norway, NoMA: If an intervention affects the HRQoL of a caregiver this can be quantified in QALYs to be used in the cost-effectiveness ratio (no specific methods for this are described in the guideline). The results of the analysis must be presented with and without the inclusion of the effect on the caregiver's QoL.
- Belgium, KCE: The effects on caregivers' HRQoL can be presented as complementary analyses but are not acceptable in the reference case.
- Japan: When the analysis from the public healthcare and long-term care payer's perspective is used, the QoL scores' influence on the informal caregiver may be considered if actual data exist.

Although there are 10 agencies that state inclusion of caregiver QoL will be considered; only the TLV in Sweden explicitly discusses the methods for how those effects are to be included.

The TLV guidelines discuss three models for inclusion of caregiver QoL: 1) additive; 2) multiplier; and 3) multicriteria. The TLV guidelines reference a report (document in Swedish) authored by Heintz, et al. [137], which explores methods from the health economics literature for incorporating informal caregivers' QoL. The guideline acknowledges limitations to the assessment methods, attributing this limitation to the lack of reliable data on the magnitude of the effect of treatment upon family members [37]. Consequently, the guideline also proposes using a standardised approximation or a standard rate as an alternative to include the QoL impact of an intervention in the economic evaluation (no details of the methodology are outlined in the guideline).

The TLV guidelines caution against double counting and distributive effects where caregiver's QoL is included in analyses; as well as the possibility of increasing uncertainty in decision-making in cases where caregiver's QoL has been included. Overall, the guidelines note that consideration of inclusion of the impacts of disease and new treatments on the QoL of the patients' family members is a new concept. Results are usually reported in a scenario analysis, but it has not formed the basis for the assessment of reasonable cost under the Pharmaceutical Benefits Act. No reimbursement decisions have been made to date using analyses which included this outcome (TLV guidelines 2022).

Valuing time for patients and caregivers

In Norway (NoMA/NIPH), the 'value of time' is calculated at a common rate for all patients and relatives regardless of their circumstances of employment. The value of time is approximately by the average salary in Norway after tax.

In Canada (CADTH) the opportunity cost approach has been proposed to place a value on a patient's or caregiver's lost time from unpaid work. This method values time spent on unpaid work based on the value of spending this time in an alternative capacity (e.g., paid work) rather than relying on the value of a market substitute (e.g., hired housekeeper). When determining the opportunity cost, the guideline suggests seeking direction from the decision-maker as to their preferred estimate of opportunity cost (e.g., average Canadian wage rate) as the estimated opportunity cost should reflect the decision-maker's equity position.

Intersectoral costs and benefits

Only three jurisdictions (Canada (CADTH); the Netherlands (ZIN); South Korea (HIRA)) describe how inclusion of intersectoral costs and benefits are factored into economic evaluation. For vaccine products, the PBAC guidelines recommend administration costs are presented separately for cost-consequence estimates (which may vary across states and territories) to government budgets beyond the health sector (e.g., clinics, community centres, schools). The MSAC guidelines recommends incorporating benefits of the test that are seen in sectors outside of health into a CCA as a sensitivity analysis. In New Zealand, PHARMAC state in their guidelines that costs to other non-healthcare government sectors occurring due to pharmaceutical funding decisions should not be included; however, may be considered if they are significant. No details are provided as to what is considered significant.

In the Netherlands (ZIN) guidelines (2016), intersectoral costs and benefits in sectors outside healthcare are considered relevant for preventative interventions, however, ZIN emphasize that the reference case should be strictly followed to allow for uniformity and comparability. The

Netherlands (ZIN) guidelines (2016) reference a guide for inclusion of these costs and benefits, which is only available in Dutch [138] and could not be reviewed; consequently, methods used to include these outcomes could not be reviewed for the purposes of this report. The ZIN guidelines do state that these outcomes are often reported as intermediate outcomes, which means that a well-grounded approach for the extrapolation to endpoints is important.

Where decisions for interventions require a broader perspective than that of the publicly funded healthcare payer, CADTH recommends conducting a CCA for the consideration of non-health benefits to complement health effects that are captured in a CUA. The CADTH guidelines also suggest that the inclusion of non-health effects could also be achieved by conducting a CBA as a non-reference case. Canada (CADTH) guidelines also mentions other methods, such as TTO or SG, to value non-health effects (e.g., criminal activity, levels of education), which can be traded-off against health before incorporation into the economic evaluation.

Value of knowing

One indirect and non-health benefit outcome assessed in Australia that differs from other agencies reviewed is the value of knowing outlined in the MSAC guidelines (MSAC 2021) [139] (e.g., the value to patients of being informed of their biomarker status). When the clinical utility of a diagnostic test cannot be determined, the MSAC may consider non-health-related benefits and harms associated with the test, which falls under the concept of the 'value of knowing'. The value of knowing incorporates any impact on the well-being of a patient beyond the changes in health outcomes that can be attributed to changes in healthcare provided (the health benefits associated with medical services), as arising from a diagnostic test. Furthermore, the benefits or harms that extend to individuals other than the patient, such as their family members or caregivers, are also considered.

The assessment of 'value of knowing' is conducted by comparing the benefits and harms of the diagnostic test with its comparator (absence of testing or a clinical diagnosis). An example is provided in Table 18.

Table 18 Example summary of benefits and harms of proposed test versus comparator

Benefit or harm	Proposed test	Comparator
Reduce the 'diagnostic odyssey'	Availability of genetic testing for pathogenic variants in the SMN1 gene in infants or children displaying unexplained hypotonia.	Imaging, nerve conduction tests, muscle biopsy, electromyography and blood tests.
Diagnostic delay	The availability of genetic testing results in earlier diagnosis. Even in jurisdictions with genetic testing, diagnostic delay is several months for SMA I and almost 4 years for SMA III. Diagnostic delay may result in psychological stress for the caregiver who is unable to determine the cause of their child's illness or access treatment to help them.	

Benefit or harm	Proposed test	Comparator
Interventions	Early diagnosis permits early intervention. Irreversible degeneration occurs in the first 6 months in SMA I. Delays in diagnosis prevent early intervention.	Delayed, may reduce efficacy of interventions. Knowing that an earlier diagnosis would have resulted in improved outcomes may result in anger or grief for a caregiver.
Access to support	Early diagnosis permits access to funding through national schemes (NDIS, carer support). Value derived from connection with others.	Delayed.
Career and life decisions	Different decisions regarding work and life are available after genetic test provides indication of prognosis.	Delayed.
Psychological impact of a diagnosis of a fatal disease	A diagnosis of SMA is accompanied with grief and psychological stress. Availability of genetic testing permits an earlier diagnosis.	Clinical diagnosis is likely to remain uncertain for some time, but will be accompanied by a similar impact as a genetic diagnosis.

Source: Table 24 of the Guidelines for preparing assessments for the Medical Services Advisory Committee. Version 1.0. May 2021.
NDIS = National Disability Insurance Scheme; SMA = spinal muscular atrophy.

To support the evidence proposed for the value of knowing benefits (or harms) quantitative or qualitative evidence can be provided. Quantitative evidence about benefits/harms is desirable but qualitative evidence may be presented in support of quantitative evidence or where quantitative evidence is of poor quality or absent. Two sources of guidance suggested in the MSAC guidelines for the use of qualitative evidence are the Cochrane Qualitative and Implementation Methods Group [140] and the National Institute for Health and Care Excellence (NICE) [141].

Conclusion

In summary, while most agencies acknowledged the importance of non-health benefits and harms in supplementary analyses, few incorporated implications beyond direct health impacts into their reference case, with some exceptions noted for specialised populations or technologies. This suggests that health outcomes remain the key factor in reimbursement decisions for the majority of interventions.

Generally, when considering indirect or non-health benefits, the agencies reviewed used both quantitative and qualitative methods to evaluate the outcomes of an intervention, summarised as follows:

- Quantitative approach: Incorporating indirect or non-health benefits quantitatively involves assigning numerical values or weights to these benefits. This could be done through the use of economic evaluation techniques such as cost benefit analysis or multi-criteria decision analysis. For example, if an intervention has potential social or economic benefits, such as increased productivity or cost savings in other sectors, these benefits can be

quantified and included in the overall assessment. Decision-makers can use specific metrics and frameworks, such QALYs, to assign a measurable value to the indirect benefits.

- Qualitative approach: Qualitative assessments involve gathering information, expert opinions, and stakeholder perspectives through methods such as interviews, surveys, focus groups, or systematic reviews of qualitative studies. These approaches help capture aspects that are difficult to quantify, such as patient experiences, societal values, and broader social impacts. Decision-makers can consider qualitative evidence alongside quantitative data to gain a more comprehensive understanding of the potential indirect benefits associated with an intervention.

The Australian guidelines are similar to those of the rest of the world in terms of considering the potential inclusion of indirect and non-health benefits and harms; noting that Sweden is currently exploring methods and considerations for inclusion of caregiver QoL (with a particular focus on evaluations in precision medicines). Although these outcomes are not considered in the base case, in general HTA guidelines are supportive of presenting these outcomes as supplementary analyses in evaluations or submissions.

Why this matters?
A societal perspective for CEA/CUA recommends inclusion of all costs and benefits, including indirect and non-health benefits and harms. Three jurisdictions (the Netherlands (ZIN); Taiwan (CDE); Sweden (TLV)) states the societal perspective is used in economic evaluation for the reference case. All other HTA agencies reviewed (including PBAC and MSAC Australia) recommend that the healthcare payer perspective is considered for the reference case. The Australian guidelines are supportive of presenting indirect and non-health benefits in applications for reimbursement as supplementary analyses. However, there are concerns pertaining to the distributional consequences of this approach in the reference case, particularly where the decision is about allocation of a constrained health care budget. For example, inclusion of productivity costs favour interventions for employed people, and may bias against interventions for children or the elderly. There is also considerable debate about appropriate methods for inclusion of indirect and non-health benefits and costs within an economic evaluation [142].

Welfare impacts of listing a new medicine on the PBS

Under Australia's PBS system, there are two relevant prices that will determine the overall impact on societal welfare of listing a new medicine. The first is the price that is agreed between the sponsor of the medicine and the government, and the second is the price the consumer pays (or the copayment, which we will call the regulated price). In Australia there are three levels of copayment, in accordance with the safety net arrangements (the general copayment, the concessional copayment and a zero copayment after the safety net threshold has been reached).

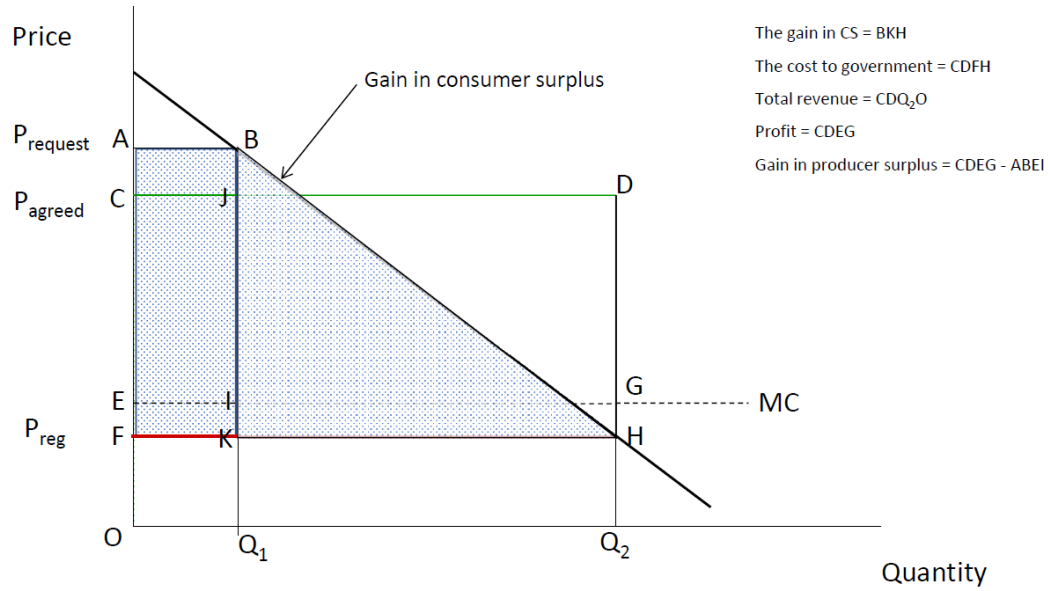
Before a medicine is listed on the PBS, if it has been approved for marketing by the TGA, there may be some demand for the medicine through the private market, but, for most new pharmaceuticals that offer a health improvement or other innovation (such as convenience in terms of mode of administration), the price in the private market tends to be prohibitively high which means that few consumers will be able to access the medicine through a private prescription. As a consequence, the revenue and therefore the profit to the sponsor, of private market sales, will be relatively small.

Once a medicine has been approved for listing on the PBS, the revenue will be determined by the agreed price, the demand at the regulated price and by any restrictions that are set by the PBAC recommendation.

This means that listing a medicine on the PBS leads to an increase in welfare to patients who are able to access the medicine at the copayment price (in economics terms this is the gain in consumer surplus). There is also an increase in revenue (and therefore profit) to the sponsor of the product. The revenue will be determined by the agreed price, and the quantity which is purchased/prescribed at the regulated price. This represents a welfare gain to the sponsor (in economic terms an increase in producer surplus).

These welfare gains to consumers and producers come at a cost to government, and ultimately to the Australian tax payers. The ultimate distribution of welfare impacts will be determined by the agreed price, but it is important to note that the welfare gains are shared between the consumers who are able to access the new medicine, and the sponsor, who makes a profit from the associated sales, with the costs being met by government (taxpayers). The distribution of welfare benefits from listing a new medicine is depicted in Error! Reference source not found..

Figure 4 Distribution of welfare impacts from a new drug listing



MC = marginal cost; $P_{request}$ = price requested by sponsor; P_{agreed} = price agreed between government and sponsor; P_{reg} = copayment.
Marginal cost in this example has been shown as constant and is indicative.

There is limited information in the market for new medicines to determine the appropriate agreed price. Health gains are often estimated in terms of gains in QALYs, but an actual market estimate of the value of an additional QALY is not possible, though the principle underlying the National Health Act is that the Australian government is willing to pay for additional health outcomes (QALYs).

For other benefits, such as convenience, one possible approach is to use stated preference methods to estimate consumer willingness to pay for this benefit. However, in eliciting such values for convenience, the estimate represents the total value of the consumer surplus associated with being able to access the medicine with the associated benefit in terms of convenience. Therefore, it that estimate of value were to be used determine the agreed price between the government and the sponsor, in effect, all of the welfare benefits from listing the new medicine would be allocated to the sponsor (and all of the cost of these welfare benefits would be paid for by taxpayers), which would mean that there was no net welfare gain to the Australian population from this recommendation.

For example, suppose the estimated average WTP for the additional benefit across all consumers who access the new medicine is $x, and this is then used to set the price increase over the comparator to be $x. It is important to note that some consumers will have a higher WTP than $x and some will have a lower WTP than $x, but the government will pay $x additional for every script (noting that all consumers who have a WTP greater than the

regulated price (the copayment) will likely access the new medicine). While there is still a welfare gain to those consumers, it is less than the additional cost to government (taxpayers) and so results in an overall welfare loss. In addition, it is important to note that consumers with a higher WTP may also have a higher ability to pay, and so using their stated WTP as part of the estimate may result in increased inequity. For this reason, while it is reasonable that the agreed price should reflect some of the welfare benefits to patients, if it captures all of these benefits, it transfers all of the consumer surplus to the sponsor with an associated cost to government (taxpayers), and may increase inequity.

Extrapolation and discount rates

It is common for clinical trials to have limited follow-up data, and therefore the full health benefits of a treatment may not be achieved within a trial period. To overcome this limitation, statistical techniques are often used to extrapolate time-to-event data beyond the duration of a clinical trial. This approach enables the estimation of long-term outcomes and costs, despite the limited availability of confirmatory clinical evidence. In HTA, extrapolation involves making assumptions about the consistency of treatment effects or cost trajectories over time, to project how a treatment or technology might perform over an extended period, which can include considerations of both clinical effectiveness and economic impact [143]. The choice of time horizon and discount rate are also interrelated with extrapolation.

Discounting is the practice of accounting for the impact of time preference when comparing cost and benefit streams, enabling a like-for-like comparison with costs and benefits that occur over disparate time periods. The choice of discount rate reflects factors such as investment opportunities and time preferences. The report on discount rates in HTA commissioned from the Centre for Health Economics Research and Evaluation (CHERE) and discussed in the July 2022, PBAC meeting is available online[5].

The time horizon for an analysis determines the length of time over which costs and benefits will be estimated. Thus, where the available (observed) data are for a period that is less than the desired time horizon (e.g., data are available from a 10-year follow-up within a study, but the desired period for analysis is a 20-year time horizon) extrapolation of the data to bridge the evidence available from the known to the desired duration is required. The need for and extent of extrapolation, has implications for the accuracy and relevance of the results. The choice of the time horizon requires justification and depends on the specific intervention being

[5] Discount rate report available from URL: https://ohta-consultations.health.gov.au/ohta/review-of-discount-rate-in-the-pbac-guidelines-pha/supporting_documents/Review%20of%20the%20Discount%20Rate%20%20Report.pdf

evaluated, population included in an analysis, the nature of the disease or condition, and the outcomes being modelled. The time horizon should be a sufficient duration to capture the differences in treatments being compared and include all relevant costs and benefits.

For example, a relatively short time horizon may be sufficient for interventions that have temporary health or QoL effects but do not impact mortality. This is because the focus is on capturing the immediate effects and short-term outcomes of the intervention. However, when there is evidence indicating that a treatment has a long-term impact on mortality or ongoing QoL effects, a lifetime time horizon may be appropriate as it allows for the comprehensive assessment of the long-term benefits and costs associated with the intervention.

A critical aspect of extrapolation exercises is estimating the expected health outcomes associated with the interventions, often using survival data expressed in terms of time-to-event. Standard statistical methods may be inadequate for analysing survival data because they are often censored, meaning that some patients may not experience the event of interest during the study period.

Comparisons of methods across jurisdictions

A comprehensive summary of the methods and processes used to extrapolate time-to-event health outcomes and costs discussed in the guidelines of the jurisdictions of interest is presented in Table 19. The subsequent sections provide detailed overview of the methods and processes employed by relevant agencies, elaborating on their respective approaches.

Table 19 Extrapolation methods for time-to-event outcomes recommended across agencies reviewed

Jurisdiction (Agency)	Extrapolation		Discount rate
	Mentioned in Guidelines	Method suggested	
England and Wales (NICE)	Yes	Fit parametric survival models to the observed data (i.e., exponential, Weibull, log-logistic, log-normal, gamma, Gompertz). More flexible extrapolation (e.g., piecewise spline models) if needed. Selection of the specific function for the base case analysis and the validation of the selected function.	3.5% for cost and benefits.
Australia (PBAC, MSAC)	Yes	As England and Wales (NICE)	5% for cost and benefits.
Scotland (SMC)	Yes	Not specified	3.5% for cost and benefits.
Canada (CADTH)	Yes	As England and Wales (NICE)	1.5% for cost and benefits.
New Zealand (PHARMAC)	Yes,	No methods specified	3.5% for cost and benefits.

Jurisdiction (Agency)	Extrapolation		Discount rate
	Mentioned in Guidelines	Method suggested	
France (HAS)	Yes	As England and Wales (NICE)	2.5% for cost and benefits the first 30 years. 1.5% for cost and benefits after 30 years.
Germany (IQWiG)	No	Not specified	3% for cost and benefits.
Norway (NoMA)	Yes	As England and Wales (NICE)	4% for cost and benefits the first 40 years, 3% from year 40 to 74 and 2% thereafter.
Sweden (TLV)	Yes	No method specified	3% for cost and benefits.
The Netherlands (ZIN)	Yes	As England and Wales (NICE)	4% for cost and 1.5% for benefits.
Belgium (RIZIV-INAMI)	No	Not specified	3% for cost and 1.5% for benefits.
Japan (C2H)	No	Not specified	2% for cost and benefits.
South Korea (NECA)	No	Not specified	5% for cost and benefits.
Singapore (ACE)	Yes.	As England and Wales (NICE).	3% for cost and benefits.
Taiwan (CDE)	No	Not specified	5% for cost and benefits.

ACE= Agency for Care Effectiveness; C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); ;CADTH= Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation (Taiwan) HAS = French National Authority for Health; IQWiG = Institute for Quality and Efficiency in Health Care (Germany); MSAC= Medical and Scientific Advisory Council; NA= not applicable; NECA = National Evidence-based Collaborating Agency (South Korea); NICE= National Institute for Health and Care Excellence; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; RIZIV-INAMI = RIZIV-INAMI= National institute for sickness and disability insurance (Belgium); SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; ZIN= The National Health Care Institute.

There was no information pertaining to extrapolation specified by these jurisdictions (Germany; Luxembourg; Belgium; Spain; Japan; Korea; Taiwan).

Source: ACE guidelines 2023, C2H guidelines 2022, CADTH guidelines 2017, CDE (TasPOR) guidelines 2006, HAS guidelines 2020, HIRA guidelines (Bae et al) 2022 , INAMI-RIZIV guidelines , IQWiG guidelines 2022, KCE guidelines 2012, MSAC guidelines 2021, NICE guidelines 2022, NoMA guidelines 2018, PBAC guidelines 2016, PHARMAC guidelines 2022, SMC guidelines 2022, TLV guidelines 2017 and ZIN guidelines 2016; Latimer TSD 14 [38].

The need for extrapolation arises where clinical trial evidence, as may be used to construct a model-based assessment of cost-effectiveness, does reflect the anticipated time horizon over which costs and outcomes may accrue. Numerous agencies have recognised the significance of extrapolation of health benefit and cost in the context of economic evaluations. Several agencies offer explicit method recommendations, with the England and Wales (NICE) TSD 14 serving as a prominent reference for guiding the extrapolation procedure (Latimer 2011). Germany stands as an exception in this regard in measures of costs and effects beyond the trial data are typically not used ([144]).

HTA agencies (Australia (PBAC); England and Wales (NICE); Canada (CADTH); France (HAS), and The Netherland (ZIN)) recommend extrapolating beyond the trial period to estimate lifetime benefits and costs when evaluating interventions that impact long term outcomes such as survival.

NICE takes various types of evidence into account during their evaluations. This includes real-world evidence, which can help improve and provide more precise estimates for economic models, such as validating extrapolation. To enhance the gathering of this real-world evidence, NICE has established a framework [145]. This framework lays out important principles for creating evidence from real-world data.

Time horizon

All agencies recommend the time horizon used in a model, as necessitating the conduct of extrapolation, to be long enough to capture all relevant benefits and costs of the intervention. Similarly, all agencies accept shorter time horizons; guidelines for Australia (PBAC/MSAC), England and Wales (NICE), Scotland (SMC), New Zealand (PHARMAC), Norway (NoMA), Sweden (TLV), and Singapore (ACE) specifically advise that a short time horizon may be appropriate for interventions not affecting mortality or with temporary health and QoL effects. France (HAS) advocate the adoption of a multigenerational time horizon[6] in the assessment of certain interventions, notably vaccines [146].

Six HTA agencies (Australia (PBAC, MSAC), England and Wales (NICE), Canada (CADTH, INESSS), Norway (NIPH)) acknowledged the importance of testing the proportional hazard assumption prior to implementing extrapolation functions to observed trial data. Restricted mean survival testing, which is an alternative measure that remains meaningful when the proportional hazard assumption does not hold, was mentioned in PBAC, CADTH, NICE and SMC guidelines. The Netherlands (ZIN) stated the time horizon should ideally cover the expected lifetime.

Table 20 Time horizon comparison across jurisdictions

Jurisdiction (Agency)	Sufficiently long enough to capture differences costs/outcomes	Advice (lifetime vs shorter time horizon)
Australia (PBAC, MSAC)	Stated	Time horizon is not extended unnecessarily
England and Wales (NICE)	Stated	Shorter where no mortality difference
Scotland (SMC)	Stated	Shorter where no mortality difference
Canada (CADTH)	Stated	Not reported.
New Zealand (PHARMAC)	Stated	Shorter where no mortality difference.
France (HAS)	Not stated	Lifetime In certain cases (such as vaccination), a multigenerational time horizon may be necessary.

[6] A multigenerational time horizon in healthcare refers to the consideration of the long-term impacts of healthcare policies, interventions, and decisions on multiple generations. This approach considers not only the immediate effects but also their consequences for future generations. It involves planning and implementing strategies that aim to improve health outcomes, prevent diseases, and enhance the overall well-being of individuals across different age groups and generations.

Jurisdiction (Agency)	Sufficiently long enough to capture differences costs/outcomes	Advice (lifetime vs shorter time horizon)
Germany (IQWiG)	Not stated	The time horizon must at least represent the average study duration. A longer time horizon should preferably be chosen in particular for chronic diseases.
The Netherlands (ZIN)	Not stated	Time horizon should preferably cover the expected lifetime
Belgium (KCE)	Stated	Shorter where no mortality difference
Sweden (TLV)	Stated	Lifetime horizon mandatory for treatments that have an impact on life
Norway (NoMA)	Stated	Short time horizon when is not realistic to use a longer time horizon
Japan (C2H)	Stated	Not reported.
Singapore (ACE)	Stated	Shorter where no mortality difference.
Taiwan (CDE)	Stated	Not reported.

ACE= Agency for Care Effectiveness; C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); ;CADTH= Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation (Taiwan) HAS = French National Authority for Health; IQWiG = Institute for Quality and Efficiency in Health Care (Germany); MSAC= Medical and Scientific Advisory Council; NA= not applicable; NECA = National Evidence-based Collaborating Agency (South Korea); NICE= National Institute for Health and Care Excellence; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; RIZIV-INAMI = RIZIV-INAMI= National institute for sickness and disability insurance (Belgium); SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; ZIN= The National Health Care Institute.
There was no information pertaining to time horizon specified by these jurisdictions (Luxembourg; Spain and South Korea).
ACE guidelines 2023, C2H guidelines 2022, CADTH guidelines 2017, CDE (TasPOR) guidelines 2006, HAS guidelines 2020, INAMI-RIZIV guidelines , IQWiG guidelines 2022, KCE guidelines 2012, MSAC guidelines 2021, NICE guidelines 2022, NoMA guidelines 2018, PBAC guidelines 2016, PHARMAC guidelines 2022, SMC guidelines 2022, TLV guidelines 2017 and ZIN guidelines 2016.Case study of extrapolation with patient-level data (NICE, TSD 14)

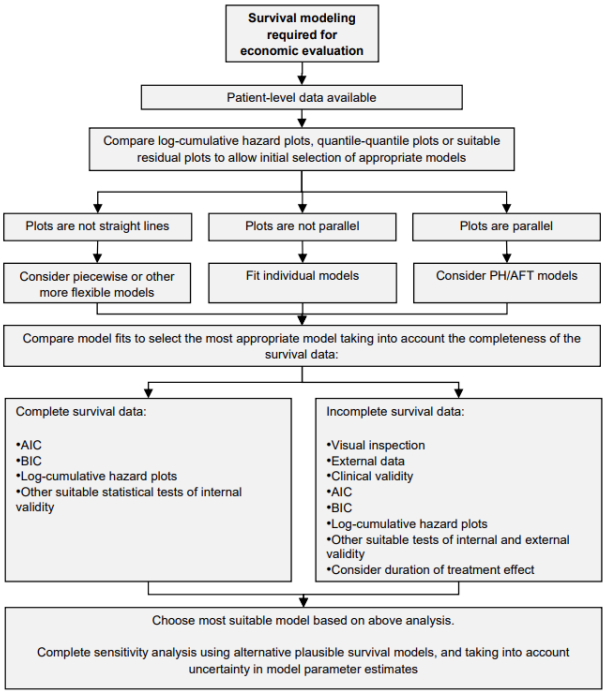
The England and Wales (NICE) TSD 14 (Latimer 2011) aimed to enhance transparency and consistency in survival analysis methods used in NICE by applying a model selection algorithm. This algorithm guides the process of fitting survival models to patient-level data within the context of an economic evaluation alongside a key clinical trial through a series of steps, Figure 5:

- Step 1: Log-cumulative hazard plots or appropriate residual plots should be generated to assess the observed hazards in the clinical trial. This helps determine the suitable type of parametric model and whether proportional hazards can be assumed. These plots also reveal situations where no single parametric model adequately fits the data.
- Step 2: If the log-cumulative hazard plots indicate approximately straight lines for any of the parametric models, those models should be fitted to the data and further assessed. If the plots for the two treatment groups exhibit parallel lines, proportional hazards models should be considered and assessed further. If the lines are not parallel, individual model fitting should be performed for each treatment arm using an appropriate model, followed by further assessment. If the log-cumulative hazard plots do not show straight lines, alternative modelling methods such as time-varying

hazards, piecewise modelling, or more flexible approaches can be considered. However, visual inspection alone should not be relied upon for model selection.

- Step 3: Models identified as potentially appropriate in Step 2 should undergo further comparison using AIC/BIC or other suitable tests of internal validity. If the data are nearly complete (most patients have experienced the event by the end of follow-up), model selection can be based on these test results and the log-cumulative hazard plots. In the presence of significant censoring, external data, clinical plausibility, and expert judgment should be employed to assess the suitability and external validity of alternative models. If the proportional hazards assumption is deemed reasonable based on the analysis in Step 2, the hazard ratio estimate should be obtained from the relevant parametric model with treatment group as a covariate. Different scenarios should be considered regarding the treatment effect over the extrapolated period.
- Step 4: Based on the above analyses, the most appropriate survival models should be selected for the base case analysis. The selection should consider the goodness of fit of the models to the observed data and the plausibility of the extrapolated portion (through the use of external data, expert judgement, biological reasoning and/or clinical validity) Similar types of models, defined by the same parametric distribution, should be used for different treatment arms unless strong evidence suggests an alternative is more plausible. In cases where multiple plausible sets of models exist, the alternatives should be included as scenario sensitivity analyses in the economic model. .

Figure 5 Survival model selection process algorithm



Source: Latimer, N. NICE DSU Technical Support Document 14.

In Australia, the PBAC guideline recommend extrapolation when differences in costs and outcomes between the intervention and comparator extend beyond for which observed data are available. When conducting extrapolation, the guideline suggests prioritising the use of observed time-to-event data until a point is reached where the observed data become unreliable due to a small number of patients remaining event-free. The chosen time point from which extrapolation is applied in the model should be validated employing external data if necessary.

When employing parametric survival curves based on the observed data, the PBAC guidelines recommend the following process:

- Determine whether assuming proportional hazards is appropriate beyond the observed data.
- Fit a variety of alternative survival models to the observed data, including exponential, Weibull, log-normal, log-logistic, gamma, and Gompertz models. Consider employing more flexible extrapolation approaches with multiple points of inflection, such as piecewise spline models, to facilitate more accurate extrapolation based on the section of the Kaplan–Meier curve that best represents long-term survival.

- Evaluate and discuss the goodness of fit using visual inspection, AIC/BIC. Justify the most suitable model for the base case and test several best-fitting models in the sensitivity analysis.
- Assess the plausibility of predictions for the unobserved period, including the ongoing hazard ratio, treatment effect, point of convergence, and residual survival in each arm. Plot the treatment effect resulting from independent extrapolation of the survival curves over the model's time horizon. If the treatment effect remains constant or increases, and this is clinically implausible, adjust the hazard ratio so that the intervention and comparator curves converge at a plausible time point.
- Consider explicit clinical decisions regarding the continuation or cessation of treatment when evaluating the extrapolated treatment effect. State and justify all relevant assumptions and ensure their consistent application when modelling treatment costs.

The PBAC guidelines are closely aligned with the NICE TSD 14 framework. Consequently, the methodologies detailed in both sets of guidelines exhibit a high degree of consistency The PBAC and all other HTA agencies reviewed draw their guidance from the NICE TSD 14, without providing the same level of detailed methodology on extrapolation, but instead, reference and rely upon the NICE TSD 14 for this aspect of their guidance.

A different approach from that recommended in Australia (PBAC/MSAC) regarding the uncertainty of the clinical trial outcomes during the extrapolation time is proposed by CADTH. Their guidelines identified two issues of central importance in this regard related to:

1. assumptions regarding the effects of treatment beyond the observed data, and
2. the effects of treatment beyond the treatment period.

In this regard, the CADTH guidelines recommend reporting and justifying the percentage of the estimated effect that occurs beyond the observed data. This can be measured as the ratio of the estimated incremental QALYs over the period of time that clinical effectiveness data are available to the estimated incremental QALYs over the entire time horizon of the model. The percentage of the estimated incremental benefit that is accumulated after treatment is stopped, should also be reported, and justified. This can be measured as the ratio of incremental QALY gains during the period on treatment to the estimated incremental QALYs over the entire time horizon of the model. The guidelines state that considering whether both these values are clinically realistic will help researchers to assess the suitability of the extrapolation methods.

Additionally, the CADTH guidelines suggests a full consideration of parameter uncertainty through a probabilistic analysis incorporating correlation with respect to the parameters within the survival function. Scenario analysis exploring structural uncertainty should be conducted using alternative plausible parametric forms, as well as comparing results with and without an assumption of proportional hazards in order to assess how well the distributions fit the observed data.

Reproducing time-to-event from published sources

When individual patient time-to-event data are unavailable, it is possible to extrapolate survival probabilities from published Kaplan–Meier curves using graph digitiser software. The England and Wales (NICE) TSD 14 (Latimer 2011) acknowledges the application of this technique without providing detailed guidance on its implementation. Only two agencies, namely ACE-Singapore and PBAC-Australia, offered insights into the appropriate use of this approach, offering similar advice in their respective guidelines.

When extrapolating survival probabilities from published Kaplan–Meier curves using graph digitiser software, the guidelines recommend fitting alternative hazard functions, such as constant (exponential) or monotonically increasing/decreasing (Weibull or Gompertz), to the extracted survival data beyond the last point of inflection until the observed data become unreliable due to a small number of patients remaining event-free. Furthermore, the guidelines recommend presenting tests to evaluate the relative and absolute goodness of fit for the chosen alternative curves to assess the validity and reliability of the extrapolated survival probabilities.

Model selection

The variety of models available for extrapolation can add to the uncertainty about future benefits and costs of the intervention under review. It is often not clear what the best model is, as hypothesis testing is not always the best way to inform the appropriate selection. Additionally, the statistics of goodness-of-fit estimated with the within-sample data, do not always predict extrapolation performance.

Statistical assessments of goodness of fit, such as AIC, BIC, and log-likelihood, assess model fit based solely on the observed period. This explains why their performance improves with data from clinical trials with longer follow-up periods. Thus model selection which relies on these goodness of fit statistics does not consider uncertainty beyond the observed follow-up period.

Models with few parameters may impose unrealistic assumptions, such as constant hazard over time. On the other hand, models with more parameters are more flexible, but require larger datasets to avoid model instability, and may lead to overfitting. Hybrid models for extrapolation have several limitations, including a loss of information and sensitivity to the choice of which data to include (i.e., bias introduced by the analyst) in the extrapolating model. Both limitations can lead to additional uncertainty in extrapolations, compared with using a single model at all time-points. Hybrid models like the piecewise spline model approach can also lead to changes in the estimated hazard in stages, which may not be clinically plausible [147].

The suitability of parametric model extrapolation to represent the observed time-to-event data and goodness-of-fit statistics will inevitably vary across diseases and patterns of treatment response. Relying solely on goodness-of-fit statistics for model selection has been found to introduce bias as it can lead to the selection of an overly optimistic model even when multiple measures agree on the optimal model [148]. Visual fit and extrapolation plausibility are commonly used in conjunction with an information criterion when selecting a parametric model. This approach is suggested by two reviews [149] [150] and can enhance the application of the information criteria. By analysing the hazard function and clinical plausibility of extrapolation, clearly implausible models for a specific disease or indication can be ruled out, preventing their selection by AIC and BIC.

Why this matters?
Economic evaluation typically requires extrapolation beyond observed data. There are two key elements – the choice of time horizon and the methodology for extrapolation. Methodology described for the extrapolation of clinical trial data in the PBAC and MSAC guidelines is consistent with HTA guidelines from other jurisdictions. The choice of time horizon depends on the nature of the disease and intervention under consideration; PBAC and MSAC guidelines advise the time horizon should not be extended unnecessarily, whereas NICE, SMC, and PHARMAC advise shorter time horizons are advised where there are no differences in mortality. The PBAC and MSAC guidelines allows for flexibility in model choices for the extrapolation of the observed clinical trials, time horizon, and validation of the modelled results. Although selection of a single 'best' model is not always possible, the approaches used in current practice is sufficiently adaptable for sponsors and decision-makers to assess the credibility of the modelled results.

Vaccines

There are specific issues that arise pertaining to the extrapolation of data for vaccines as the benefits occur in the future. In the Australian context, the ATAGI plays a pivotal role in advising on how the benefits of vaccines are assessed in the future. Sponsors/manufacturers are required to seek advice from ATAGI on issues such as the applicability of effectiveness estimates in varying populations or settings, the validity of clinical predictions based on surrogate outcomes, and the extrapolation of effectiveness over time or throughout the community and/or select subpopulations within the community. ATAGI also provide specific advice on underlying assumptions regarding herd immunity, age-effects and any assumptions about key vaccine-related parameters that would be incorporated into cost-effectiveness modelling [39]. For example, estimating vaccines efficacy over extended time periods such as the waning of treatment effect; seroconversion rates, and impact of emerging variants.

ATAGI's guidance to PBAC is instrumental in addressing questions about vaccine effectiveness across diverse populations, the reliability of predictions based on surrogate outcomes, and the extrapolation of vaccine effectiveness over time and within the community. This differs from England and Wales, where NICE only evaluates therapeutic vaccines; and for other vaccine categories, the responsibility falls under the Joint Committee on Vaccination and Immunisation (JCVI) with different sets of HTA requirements.

Discount rate

The theoretical foundation for discounting in economic evaluation is shaped by economic theories such as Ramsey's theory of saving and Samuelson's discount utility model [151, 152]. The discounting process assumes that society's preference for immediate gratification can be encapsulated in a single discount rate. The selection of an appropriate discount rate is challenging, with varying recommendations and conflicting advice across different sources. One approach sets the discount rate based on the social opportunity cost—reflecting the rate of return forgone due to public spending diverting resources from the private capital market [153]. Another approach, social time preference, considers factors like immediate utility preference, potential risks, changing preferences, technological shifts, and macroeconomic factors [154].

As shown in the CHERE review of the discount rate in the PBAC Guidelines [40] (previously reviewed by PBAC), the majority of jurisdictions apply the same rate to costs and benefits, although rates do differ across jurisdictions. Among the 19 jurisdictions included in this analysis, current discount rates for costs range from 1.5% to 5%, with 3% and 5% being the most common (5 of 19 and 5 of 19 (26%), respectively). Discount rates for health benefits also range

from 1.5% to 5%, with 3% and 5% being the most common (5 of 19 and 5 of 19 (26%), respectively). Most of the jurisdictions listed in have consistently applied equal discounting to costs and health benefits since 1990, with the exception of Belgium (which currently applies differential discounting) and France and the UK (both of which recommended differential discounting at some point in the past, but currently recommend equal discounting).

The CHERE report found that, of the 19 jurisdictions included, reference-case differential discounting of costs and health benefits is currently only used in Belgium and the Netherlands. In both jurisdictions, HTA guidelines recommend the discounting of health benefits at a lower rate than costs, premised on the value of health increasing over time and policy support for preventive interventions (e.g., screening, vaccination) that generate benefits over the long term [153, 155, 156].

The majority of agencies reviewed were aligned with the PBAC/MSAC recommendation of fixed discount rate in time. Of the national health economic evaluation guidelines reviewed in the report, only three jurisdictions explicitly allow for time-variable discount rates, with reduced rates to be applied in prescribed circumstances: Thailand (time horizon of > 30 years: 4% costs, 2% health benefits) [156]; the UK (long-term benefits of at least 30 years: 3.5% costs, 1.5% health benefits) [157]; and France (time horizon > 30 years, no less than 2% costs and health benefits) [156]. HTA guidelines in Scotland specify a discount rate of 3.5% for costs and benefits for a time horizon of up to 30 years.

A discount rate is the rate of return used to discount future costs and benefits back to their net present value. The choice of discount rate reflects factors such as investment opportunities and time preferences. This is one of the key parameters often specified in HTA guidelines for use in the conduct of economic evaluations, which factors into reimbursement decisions. The choice of discount rate can have a substantial impact on the estimated cost-effectiveness of a health intervention. All else being equal, applying a lower discount rate implies more value is placed on interventions that are preventative, relative to those associated with treatment, or that claim a long-term future stream of benefits relative to costs.

The report highlighted that there was minimal evidence provided of the underlying rationale for jurisdictions' choice of a discount rate in the literature; the most common stated reasons include consistency with existing recommendations and central governments' cost of borrowing [155-157].

Why this matters?
Currently the PBAC and MSAC guidelines specify the discount rate required in economic evaluations. Previously, the PBAC advised that if the Government makes a broader policy decision to change the standard base-case discount rate for economic evaluations of health interventions the base-case discount rate should be no lower than 3.5% - 4% per year and a mandatory 5% discount rate sensitivity analysis would need to be conducted for purpose of being explicit about the impact on opportunity cost and budget, and to ensure consistency with prior decisions by allowing advisory committees to compare ICERs for new listing requests with previously considered items based on the 5% rate.

Conclusion

In July 2022, an inquiry was initiated with the PBAC to ascertain the alignment of the discount rate stipulated in the PBAC Guidelines (Version 5.0, 2016) with international best practice. Following a comprehensive assessment involving the review of a prepared report, dual-phase stakeholder consultation, and the input from esteemed entities such as the PBAC Economic Sub-Committee (ESC), MSAC evaluation sub-committee, and the Australian Technical Advisory Group on Immunisation (ATAGI), the PBAC reached a decision against endorsing an isolated modification to the foundational discount rate stipulated in its Guidelines [158].

The PBAC concluded [158] that if the Government make a broader policy decision to change the standard base-case discount rate for economic evaluations of health interventions the base-case discount rate should be no lower than 3.5% - 4% per year and a mandatory 5% discount rate sensitivity analysis would need to be conducted for purpose of being explicit about the impact on opportunity cost and budget, and to ensure consistency with prior decisions by allowing advisory committees to compare ICERs for new listing requests with previously considered items based on the 5% rate.

The use of the methods described in the England and Wales (NICE) TSD 14 to guide the section of model to extrapolate the trial data is common to the majority of guidelines reviewed. Although the steps described in the document include clinical validity and examination of hazard plots, the application of the method usually rely on AIC and BIC. In the UK, a review of submission between 2011 (the year the TSD was published) and 2017 [150] revealed a significant proportion (91%) of submissions compared various standard parametric models based on AIC and BIC, however, a smaller number of submissions (38%) took into account the shape of the hazard function, and only a minority of TAs (40%) attempted to validate the extrapolated portion of the survival function using external data.

The review of international guidelines and academic literature showed Australia's approach to extrapolating healthcare benefits and discounting, outlined in the PBAC and MSAC guidelines, is consistent with global standards. Additionally, Australia's framework for extrapolation does not prevent sponsors from applying different methods in their submissions from those mentioned in the guidelines, allowing for a comprehensive examination of evidence.

Assessment of economic uncertainty in Australia and internationally

There are various sources of economic uncertainty within HTA, which have been described to fall across three broad categories [159]:

- Methodological uncertainty: There are different normative views about what is the 'best' approach for economic evaluations to inform optimal decision-making [160]. This includes the perspective taken (e.g., healthcare vs societal), the time-horizon and discount rates used, the types of disease outcomes captured (e.g., mortality, morbidity, quality-of-life) and whether costs and health outcomes for caregivers should be included.
- Structural uncertainty: This relates to the range of assumptions and judgements required in constructing an economic model. This includes the selection of relevant comparators, the inclusion or exclusion of relevant events (such as the assumed standard pathway of care or which disease states to incorporate) and the translation of clinical data for incorporation in the model (for example transformation of a continuous outcome to a dichotomous outcome or a surrogate to a final outcome, extrapolation of data beyond the trial) [161].
- Parameter uncertainty: This refers to the uncertainty about the mean values of parameters included in an economic model (for example health outcomes, utilities and resource use) [159].

Methodological uncertainty

Methodological uncertainty is usually dealt with by HTA bodies through prescription of a ‘reference case’ , which allows for consistency between submissions and assessment of evidence [160]. Of the HTA guidelines reviewed, nine jurisdictions define a reference case that specify accepted methods for economic evaluations (Australia (MSAC); England and Wales (NICE); Canada (CADTH); Norway (NoMA/NIPH); France (HAS); the Netherlands (ZIN); Belgium (KCE); Singapore (ACE)). Other jurisdictions also outline preferred methods for economic

evaluations; however, these are referred to as part of a 'base case' analysis (Australia (PBAC); Germany (IQWiG); New Zealand (PHARMAC); Japan (NIPH); South Korea (HIRA)). Scotland (SMC), and Taiwan (CDE) require Sponsors to submit economic evaluations consistent with their guidelines, however these are not specified as either a reference case or base case. The HTA guidelines for Sweden (TLV) are described as general advice that should not be understood as a manual but rather as support for Sponsors when designing applications. For all jurisdictions, deviations from reference or base case methods are permitted but should be clearly specified and justified. Additionally, several guidelines recommend sensitivity analyses be undertaken to assess the impact of methodological choices, in particular exploring alternative discount rates (Australia (MSAC/PBAC); England and Wales (NICE); Scotland (SMC); Canada (CADTH); New Zealand (PHARMAC); Belgium (KCE); France (HAS); Germany (IQWiG); Spain (HTAA); Sweden (TLV); Japan (C2H); Korea (HIRA); Singapore (ACE); Taiwan (CDE)).

Structural uncertainty

Several guidelines recommend that structural uncertainty be assessed through scenario or sensitivity analyses using alternative plausible assumptions (Australia (MSAC/PBAC); Scotland (SMC); New Zealand (PHARMAC); France (HAS); Germany (IQWiG); Netherlands (ZIN); Norway (NoMA/NIPH); Japan (C2H); Singapore (ACE)). However, only England and Wales (NICE), Canada (CADTH) and Belgium (KCE) recommend that these be performed probabilistically.

Parametric uncertainty

All guidelines recommend that parametric uncertainty be assessed through some form of sensitivity analysis. Some jurisdictions prefer deterministic sensitivity analyses (univariate/multivariate) to identify the most influential parameters on cost-effectiveness results (Australia (MSAC/PBAC); Scotland (SMC); New Zealand (PHARMAC); Spain (HTAA); France (HAS); Singapore (ACE); Taiwan (CDE)) while other jurisdictions prefer probabilistic sensitivity analysis be undertaken to assess the simultaneous impact of variations in several parameters (England and Wales (NICE); Canada (CADTH); Belgium (KCE); Japan (C2H)). Norway (NoMA/NIPH), the Netherlands (ZIN) and Korea (HIRA) recommend that both deterministic and probabilistic sensitivity analyses be undertaken, while England and Wales (NICE) suggest a threshold analysis as an option to explore highly uncertain parameters when identifying a parameters 'switching value' (the value a parameter required to meet the explicit cost-effectiveness threshold set by NICE).

Table 21 Methods for addressing economic uncertainty across jurisdictions (agencies)

Jurisdictions (Agency)	Methodological uncertainty	Structural uncertainty	Parameter uncertainty
Australia (MSAC/PBAC)	Specified reference case (MSAC) Preferred methods for base case analysis (PBAC) Guidelines recommend presenting sensitivity analyses for discount rate (0% and 3.5%) and time-horizon (using plausible alternatives).	Use scenario analyses to assess the impact of assumptions regarding the structure of the economic model.	DSA preferred (univariate/multivariate); PSA optional
England and Wales (NICE)	Specified reference case.Uncertainty about the appropriateness of the methods used in the reference case can be dealt with using sensitivity analyses (including alternative discount rate of 1.5%).	Explore the effect of structural uncertainty through scenario analyses. In general, scenario analyses should also be probabilistic. When only deterministic base-case or scenario analyses are provided, this should be justified.	PSA preferred; DSAs exploring individual or multiple correlated parameters may be useful for identifying parameters to which the decision is most sensitive; Threshold analysis can be used as an option to explore highly uncertain parameters.
Scotland (SMC)	Requires Sponsors to submit economic evaluations consistent with their guidelines. Uncertainty about the appropriateness of the methods used can be dealt with using sensitivity analyses (including alternative discount rates between 0% and 6%).	Characteristics of the model subject to uncertainty should be formally examined using sensitivity analyses.	DSA (one-way and two-way) preferred
Canada (CADTH)	Specified reference case Methodological uncertainty should be explored by comparing the reference case results to those from a non-reference case analysis (including using alternative discount rates of 0% and 3%).	Structural uncertainty should be addressed using scenario analysis. Probabilistic analyses should be presented for each scenario.	PSA preferred.
New Zealand (PHARMAC)	Preferred methods for base case analysis. Suggested to present sensitivity analyses using alternative discount rates of 0% and 5%	It is recommended that structural uncertainty be formally examined in sensitivity analyses.	DSAs (univariate/ multivariate) required; PSA should be considered for detailed analyses
Belgium (KCE)	Specified reference case Methodological uncertainty from reference case can be assessed through scenario analyses (including alternative discount rates of 0%, 3% and 5%).	Structural uncertainty is dealt with in scenario analyses, which should be performed probabilistically.	PSA preferred

Jurisdictions (Agency)	Methodological uncertainty	Structural uncertainty	Parameter uncertainty
France (HAS)	Specified reference case Sensitivity analyses should be conducted to quantify the impact of the methodological choices made for the reference case analysis (including alternative discount rates of 0% and 4.5%).	Sensitivity and scenario analyses should be conducted to quantify the impact of structural uncertainty on the results of the evaluation.	DSAs (univariate/ multivariate) should systematically be conducted to identify the parameters that have the greatest impact on the results of the evaluation.
Germany (IQWiG)	Preferred methods for base case analysis. Suggests presenting sensitivity analyses using alternative discount rates (0% and 5%)	Structural sensitivity analyses are performed to investigate the impact of a variation of assumptions in the model structure	Both univariate/multivariate DSAs as well as PSAs can be presented.
Netherlands (ZIN)	Specified reference case	Should be addressed through scenario analyses	Both PSA and DSAs should be done
Norway (NoMA/NIPH)	Specified reference case	Scenario analyses should be undertaken using plausible alternatives.	Both PSA and DSAs should be done
Spain (HTAA)	Specified reference case Recommended to present sensitivity analyses using alternative discount rates of 0% and 5%	Not specified	DSAs (univariate/ multivariate) must be carried out; whenever feasible, PSA should be added
Sweden (TLV)	Not specified- general advice provided for support in designing applications. Suggested to present sensitivity analyses using alternative discount rates of 0% and 5%	Not specified	Sensitivity analyses of central assumptions and parameters is important (not further specified)
Japan (C2H)	Preferred methods for base case analysis For situations in which uncertainty is high because of a long time-horizon, a shorter-term analysis is necessary (such as the period for which clinical study data are available). Sensitivity analyses using alternative discount rates (0% and 4%) should be presented.	If the analysis setting has multiple scenarios and this could affect the results, a scenario analysis should be conducted.	PSA preferred
Korea (HIRA)	Preferred methods for base case analysis Sensitivity analyses using time-horizon equivalent to the length of the clinical trial and alternative discount rates (0% and 3%) should be presented	Not specified	DSAs (univariate/ multivariate) and PSA recommended
Singapore (ACE)	Specified reference case Other scenarios can be presented to test sensitivity of results to discount rate applied	Should be explored through plausible scenario analyses	DSAs (univariate) should be presented for each uncertain parameter in the economic evaluation.

Jurisdictions (Agency)	Methodological uncertainty	Structural uncertainty	Parameter uncertainty
	(alternative rates not specified).		Multivariate or PSA may also be performed (not mandatory)
Taiwan (CDE)	Requires Sponsors to submit economic evaluations consistent with their guidelines. Sensitivity analyses using alternative discount rates between 0-10% is suggested	Not specified	DSAs (univariate/ multivariate) only

ACE = Agency for Care Effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Centre for Drug Evaluation (Taiwan); DSA = deterministic sensitivity analysis; HAS = French National Authority for Health; HIRA = Health Insurance Review and Assessment Service (South Korea); HTAA = Health Technologies Assessment Agencies (Spain); IQWiG = Institute for Quality and Efficiency in Health Care (Germany); KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); PSA = probabilistic sensitivity analysis; SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); ZIN = National Health Care Institute, the Netherlands.
Source: Guidelines: NICE guidelines 2022; SMC guidelines 2022; PHARMAC guidelines 2015; HAS guidelines 2020; IQWiG General Methods 2022; NoMA (pharmaceuticals) guidelines 2018; NIPH guidelines 2021; ZIN guidelines 2016; KCE guidelines 2012; C2H guidelines 2022; PBAC guidelines 2016; MSAC guidelines 2021; CADTH guidelines 2017; TLV guidelines 2017; HTAA guidelines (Lopez-Bastida et al) 2010; HIRA guidelines (Bae et al) 2022; ACE (medical technologies) guidelines 2022; CDE (TasPOR) guidelines 2006. Conclusion

All HTA guidelines recommend identifying sources of uncertainty in economic evaluations (methodological, structural and parametric) and undertaking additional analyses to assess their impact on cost-effectiveness estimates. While there are some minor differences in the extent to which submissions are required to conform to a prescribed 'reference case' or 'base case', all guidelines allow for deviations if they can be justified. Additionally, while there is heterogeneity in preferred methods to address parametric uncertainty (deterministic vs probabilistic sensitivity analyses), most guidelines (including Australia (MSAC/PBAC)) provide the option to present both methods.

Why this matters?

Prescription of a 'reference case' can be used to reduce methodological uncertainty in economic evaluations, improving consistency and comparability of cost-effectiveness estimates between submissions. In Australia, the MSAC describes a reference case for economic evaluations, while the PBAC specifies how certain aspects of the economic evaluation should be undertaken as part of a 'base case' analysis. However, both guidelines allow for flexibility from the prescribed reference/base case.

This flexibility is important, as reference case methods may not be appropriate, or fit for purpose, depending on characteristics of the health technology, data availability or the patient population. Further, reference case methods can become outdated compared to developments in the literature, while changes in healthcare policies, funding structures, and societal values

can introduce shifts in priorities, rendering certain aspects of existing reference cases less applicable or even obsolete.

Moving forward, regular reviews of the reference case for MSAC and base case for PBAC are warranted to ensure that evaluation frameworks remain relevant and reflect the evolving healthcare environment in HTA.

6. Findings Part 2: Special considerations for particular technology of populations types and sizes

Rare diseases and small patient populations

Treatments for rare diseases and small patient populations pose significant challenges for HTA methods and processes [162]. Products developed to treat rare diseases may have higher drug acquisition costs, due to expenditure in research and development coupled with low patient volumes. To encourage research and development for rare diseases, regulatory authorities have introduced incentives for orphan products e.g., granting orphan drug designation, market exclusivity, and corporate tax incentives [41]. Treatments for rare diseases are often registered under provisional or conditional approval pathways and where lower levels of clinical evidence may be accepted.

Orphan drug designation may be given by regulatory authorities governing medicines/health technologies. Medicines requesting orphan drug designation must meet a number of criteria. For example criteria applied by the TGA include: 1) medicine is intended for the treatment, prevention or diagnosis of disease that is life-threatening or chronically debilitating; 2) the target population is very small defined by a low prevalence and/or individuals requiring supply (i.e.,<5 in 10,000 people); 3) there is a lack of financial viability i.e., if it is unlikely that marketing the medicine would yield enough returns to justify the investment required for its development [163, 164]. However, lowering evidence requirements for marketing authorisation results in higher clinical uncertainty, thus presenting challenges for HTA of these products [165]. Limitations in the available clinical and safety data for rare diseases and small populations impacts on the robustness of the conduct of economic evaluations e.g., such as use of single-arm studies, smaller sample sizes, heterogenous population, use of surrogate measures, or shorter duration of patient follow up, reliance on the immature clinical evidence, to inform modelling. As one of the major factors considered for reimbursement pathways is cost-effectiveness, there is concern that this may limit access to treatment for rare diseases.

Rare diseases are a disparate group of disorders that can affect any body system. Most rare diseases have a genetic association and are often severely debilitating; they impair physical and mental abilities and shorten life expectancy. It is commonly quoted that, combined, rare

diseases affect 6–8% of the population; however, there are limited data supporting this figure [166]. The definition of a rare disease depends on its prevalence or the count of individuals affected by the condition, usually a small patient population.

Definitions

A universal definition of 'rare disease' has not yet emerged, and consequently, there is no corresponding universal definition for therapies for the treatment of rare diseases. Medicines used to treat rare disease may be assigned an orphan drug designation, where additional criteria must be met to obtain an orphan drug designation status from a regulatory authority governing medicines/health technologies. The definitions used for orphan drugs or rare diseases are often inconsistent from country to country [41].

Rare diseases are characterised by a low prevalence (noting there is a distinction in prevalence estimates pertaining to definitions for ‘rare’ and ‘ultra-rare’). The Australian DoHAC considers a disease rare if it affects fewer than 5 in 10,000 people (or 50 in 100,000) [42]. Other jurisdictions that use a similar definition of rare disease include Canada [167], European Commission for European jurisdictions [41, 168], and Singapore (Ministry of Health). In Taiwan a rare disease is defined as one affecting not more than 1 in 10,000 patients [169]. Jurisdictions such as Japan and South Korea use a fixed number of patients. In Japan, an orphan drug is one that treats fewer than 50,000 patients, while in South Korea a rare disease affects fewer than 20,000 people (Japan MHLW; South Korea, Rare Disease Management Act; [170] [169]). A subset of ultra-rare diseases has been defined as those with a prevalence of fewer than 1 in 50,000 patients, and is used in Australia in the Life Saving Drugs Program (LSDP) [43], New Zealand (PHARMAC) [171], European Union [172] and Scotland (SMC) [4].

The additional definitions can include drugs that treat serious, disabling, or life-threatening conditions, where there are no other realistic treatment options for that condition (Australia (LSDP); Canada (CADTH); Germany (IQWiG); Singapore (Ministry of Health) [173]; Spain [174]).

Comparisons of HTA methods and processes across jurisdictions

To address the specific challenges posed by limited evidence generation for rare diseases treatments, regulators and HTA agencies have started implementing specific policies to assess these technologies.

In most jurisdictions, orphan drug products must undergo formal HTA economic evaluation after regulatory approval to gain reimbursement (New Zealand (PHARMAC), England and Wales (NICE), Scotland (SMC), Canada (CADTH), Belgium (KCE), Norway (NoMA), Sweden (TLV),

Singapore (ACE), Japan (C2H), South Korea (HIRA), Taiwan (NIHTA). A few jurisdictions, including Australia, have parallel processes in place for registration and reimbursement (Australia (TGA and PBAC); The Netherlands (Medicines Evaluation Board (MEB) and ZIN); England and Wales (NICE)). There are no differences in the way orphan drug products and other pharmaceutical products are processed from this regard.

The EMA can provide parallel regulatory–HTA scientific advice to allow manufacturers to receive simultaneous feedback from both EU regulators and HTA bodies on development plans for new medicines [175] . This initiative is led by European HTA bodies that include Spain (AEMPS), Germany (GBA and IQWiG), France (HAS), Belgium (KCE), Norway (NoMA) and Sweden (TLV). Tafuri et al (2016) showed that at least eight HTA bodies participated in this parallel scientific advice, that included England and Wales (NICE), Germany (GBA), Sweden (TLV), France (HAS), Spain (CAHIAQ) and Belgium (INAMI). Singapore (ACE) allows a medicine to be either registered by the Health Sciences Authority Singapore or a reputed international regulatory authority (US (FDA), Europe (EMA)) before commencement of the HTA process ([176], Singapore (ACE)). Overall, there appears to be no differences in the way orphan drug products and other pharmaceutical products are processed from this regard.

Programs enabling early access to treatment for rare diseases are available in many jurisdictions. These programs tend to be funded in a variety of ways (pre-marketing, pre-reimbursement, clinical trial participation, compassionate use programs). Besides pre-market authorisation programs, early access routes include off-label use, named patient basis program and compassionate use programs.

Eleven jurisdictions had some specifications in HTA guidelines or had programs applicable to health technologies for rare diseases (Australia (PBAC/LSDP); England and Wales (NICE); Scotland (SMC); Canada (CADTH); New Zealand (PHARMAC); France (HAS); Germany (IQWiG); Belgium (KCE); Singapore (ACE); South Korea (NECA); Taiwan (CDE, NIHTA, NIHA and HPA)). Three jurisdictions have specific pathways for ultra-orphan treatments (Australia; England and Wales; Scotland).

The methods, processes and programs across jurisdictions noting special considerations for rare diseases and small populations are presented in Table 22.

Table 22 Summary of pathways, programs and funding by jurisdiction

Jurisdiction (HTA Agency)	Pathways, committees, and meetings	Funding program/organisation
Australia (PBAC/LSDP)	Pathways: 1. Rule of rescue process within PBAC (must meet four factors);	No separate fund. While there is not a distinct pool of funding for LSDP, it is a separate

Jurisdiction (HTA Agency)	Pathways, committees, and meetings	Funding program/organisation
	2. LSDP (for ultra-rare, life-threatening conditions only) Orphan drugs or other medicines for rare disease not meeting criteria for 'rule of rescue' or LSDP follow the pathways as for other medicines.	program to the PBS and legislation governing the PBS does not apply LSDP.
England and Wales (NICE)	Highly Specialised Technology (HST) Program for very rare and often very severe (i.e., ultra-rare) disease. Highly specialised technologies evaluation committee (HSTEC) is a standing advisory committee of NICE). Technologies must fulfil selection considerations.	Innovative Medicines Fund
Scotland (SMC)	Ultra-Orphan Pathway for end of life or ultra-rare disease. Patient and Clinician Engagement Process (PACE) meeting can be convened during reassessment stage.	New Medicine Fund. Ultra-Orphan Drug Risk Share provides funding for: 1) Medicines approved under ultra-orphan pathway; and 2) small number of extremely rare conditions accepted by SMC outside of the ultra-orphan pathway process.
Canada (CADTH)	No separate review processes as for other medicines. 1. Considerations for Significant Unmet Need are identified during CADTH drug review processes. CADTH Reimbursement Guidelines also note that rarity of the condition is not a sole consideration but use an example to illustrate considerations (e.g., for disease with fewer than 5 in 10,000 patients). 2. Oncology drugs review via separate pathway: pan-Canadian Oncology Drug Review (pCODR). The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) provide reimbursement recommendations.	Each provincial and territorial government offers a drug benefit program for eligible recipients. Prescription drugs administered in Canadian hospitals are provided at no cost to the patient.
New Zealand (PHARMAC)	No separate review processes as for other medicines. Rare Disorders Subcommittee of PTAC, base the decision using factors for consideration with most relevant to rare disorders being: health need of the person, availability and sustainability of existing medicine, and health needs of others (such as carers of people with rare disorders), ad well the subcommittee's clinical expertise.	No separate fund
France (HAS)	• Medicines: Early Access Authorisation for medicinal products for severe, rare or incapacitating disease that have not yet received marketing authorisation. • Devices: Temporary coverage allows for devices to be reimbursed for one year, pending conventional reimbursement process).	No separate fund
Germany (IQWiG)	Orphan drugs are exempt from benefit assessment procedure if the annual turnover is below € 50 million.	No separate fund
Belgium (KCE)	Orphan drugs are exempt from submitting a pharmacoeconomic evaluation. A budget impact analysis is required.	Special Solidarity Fund (if market access was granted)
Singapore (ACE)	No separate review processes, however, HTA process is conducted in consultation with the Rare Disease Expert Working Group.	Rare disease fund (a national multi-stakeholder charity fund, Community to Government donations (1:3), for a limited list of conditions). Financial support for each eligible patient is determined according to their needs on a case-by-case basis. It is intended to be a last-line of support after

Jurisdiction (HTA Agency)	Pathways, committees, and meetings	Funding program/organisation
		government subsidies, insurance and other financial assistance.
South Korea (NECA)	Orphan drugs, and drugs for life-threatening conditions for which comparable treatment do not exist are exempt from pharmacoeconomic review.	Additional financial support from Government based on Rare Disease Management Act (budget or the National Health Promotion Fund)
Taiwan (CDE, NIHTA, NIHA and HPA)	Taiwan Food and Drug Administration expedited programs for marketing approval. Applications for processes are subject to qualifying criteria 1. Priority Review: for drug intended to treat a serious condition and address unmet clinical need with major clinical advance– review time 240 days; 2. Accelerated Approval: criteria as for Priority Review plus an orphan drug designation in US, UK, Japan, Switzerland, Canada, France, Australia, Germany, Belgium, and Sweden or addressed unmet clinical need with difficulties of manufacturing or importing – review time 240 days; 3. Breakthrough Therapy: to treat serious condition or rare disease, substantial improvement over available therapies; and at least one clinical trial conducted in Taiwan– review time 240 days;.	Additional funding provided by HPA for orphan drugs not covered by National Health Insurance

ACE = Agency for Care effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CDE = Center for Drug Evaluation (Taiwan); HPA = Health Promotion Administration (Taiwan); INESSS = National Institute of Excellence in Health and Social Services (Canda, Quebec); IQWiG = Institute for Quality and Efficiency in Health Care (Germany); KCE = Belgian Health Care Knowledge Centre; LSDP = Life Saving Drugs Program (Australia); NECA = National Evidence-based Collaborating Agency (South Korea); NICE = National Institute for Health and Care Excellence (England and Wales); NIHA = National Health Insurance Administration (Taiwan); NIHTA = The National Institute for Health Technology Assessment (Taiwan); PBAC = Pharmaceutical benefits Advisory Committee (Australia); pCORD = pan-Canadian Oncology Drug Review; PHARMAC = Pharmaceutical Management Agency, (New Zealand); Pmda = Pharmaceutical and Medical Devices Agency (Japan); PTAC = Pharmacy Technician Accreditation Commission (New Zealand); SMC = Scottish Medical Consortium; Zorginstituut Nederland = National Health Care Institute (The Netherlands).
There was no information pertaining to pathways available for rare diseases for Spain.
There was no separate review process specified by these jurisdictions (France, Netherlands, Luxemburg, Norway, Sweden, and Japan).
Source: Australia TGA [164], LSDP guidelines [43], PBAC Guidelines [72]; England and Wales:[177-179]; Scotland: [180-182]; Canada: [6, 183]; New Zealand: [171]; France: [184, 185]; Germany: [186-188]; The Netherlands: [189]; Belgium: [14]; South Korea: [170, 190]; Singapore: [173, 176]; Taiwan: [191, 192].

Special considerations for economic evaluation/processes

Several jurisdictions apply explicit criteria for rare disease or orphan drugs during the HTA process (Australia (LSDP); England and Wales (NICE), Scotland (SMC), Sweden (TLV), Germany (IQWiG) and Belgium (KCE)).

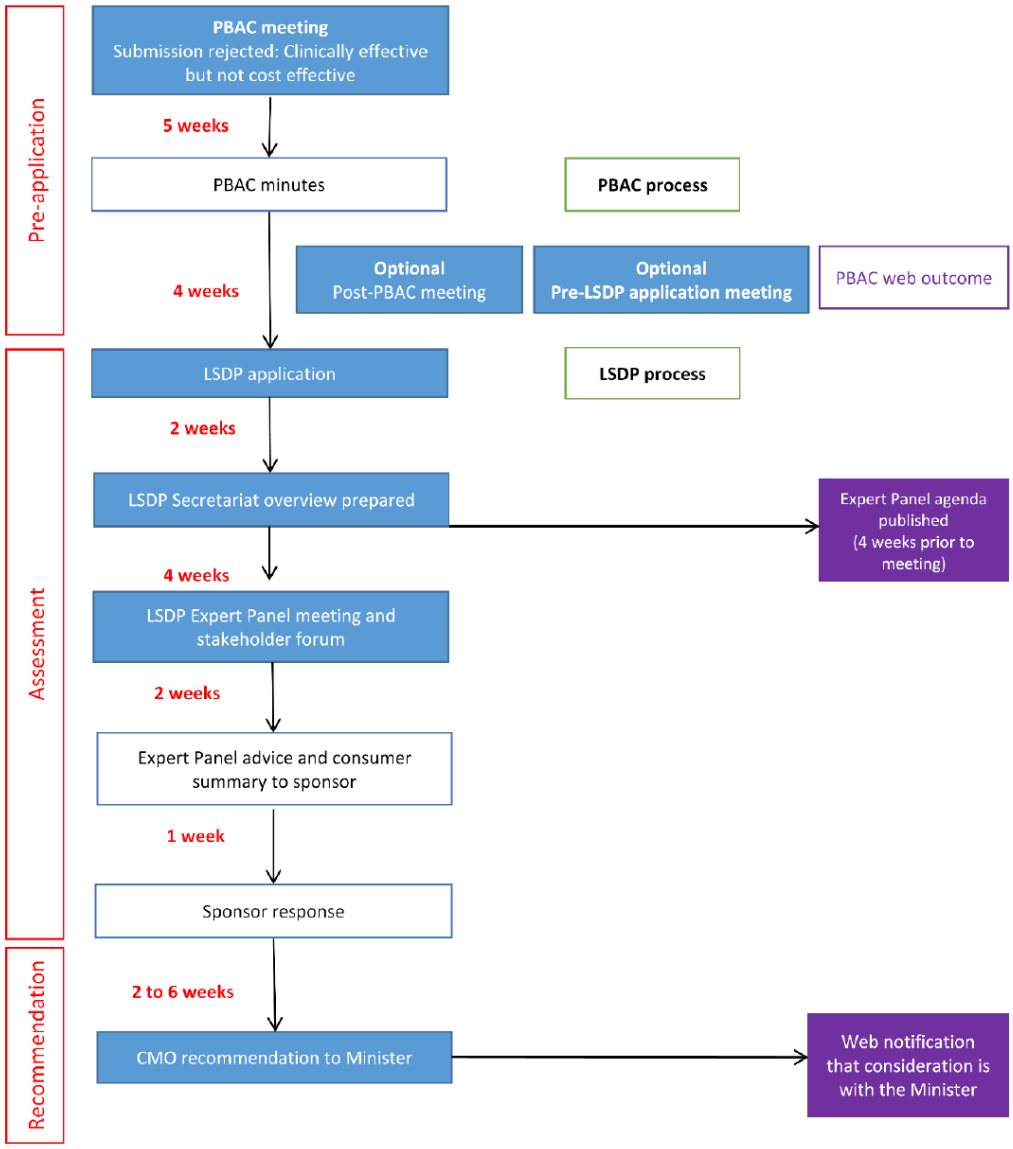
Australia (PBAC/LSDP and MSAC)

In Australia, medicines for ultra-rare and life-threatening diseases are predominantly paid for by the Commonwealth via the LSDP the PBS; but may be funded via joint Commonwealth and Jurisdictional funding arrangements under the National Health Reform Agreement. Before being considered for inclusion on the LSDP, a drug must first be considered by the PBAC. The PBAC must consider the drug is clinically effective, but reject the drug for PBS listing due to the drug

not being cost-effective. The sponsor can then seek advice from the DoHAC pertaining to the approach to be taken for preparing an application to the LSDP.

Applications to the LSDP must meet all of the criteria as outlined in the procedure guidance [43] including that: 1) TGA approval for the requested indication; 2) the disease is identifiable with reasonable diagnostic precision; 3) epidemiological and other studies provide evidence that disease causes a significant reduction in age-specific life expectancy; 4) there is evidence to predict a patient's lifespan will be substantially extended as a direct consequence of the use of the drug; 5) the drug is clinically effective but rejected for PBS listing because it fails to meet cost-effectiveness; 6) there are not alternative drugs listed on the PBS or available for public hospital in-patients. However, new medicines can be included on the LSDP if there are already other LSDP medicines that treat the same condition; 7) there are no non-drug treatments that medical authorities recognise as suitable cost-effective treatments for the condition; and 8) the cost of the medicine (defined as cost per dose multiplied by the expected number of doses in a one year period) would be an unreasonable financial burden for the patient or their guardian. All applications seeking funding through the LSDP are considered by the LSDP Expert Panel [43]. The procedure for the consideration of new medicines requesting listing on the LSDP is provided in Figure 6.

Figure 6 Procedure for consideration of new medicines for subsidy through the LSDP



CMO = Chief Medical Officer; LSDP = Life Saving Drugs Program; PBAC = Pharmaceutical Benefits Advisory Committee;
Source: Procedure guidance for medicines funded through the Life Saving Drugs Program (LSDP) version 1.0, July 2018.

The LSDP pertains to drugs targeting ultra-rare and life-threatening diseases [43]. However, within PBAC, which lacks a distinct protocol for rare diseases outside of the LSDP, there is a provision for 'rule of rescue' process that underlines the value of preserving life, regardless of treatment expenses. The rule of rescue introduces a set of criteria that, when satisfied, permits flexibility in exceptional situations and can significantly influence reimbursement decisions. These criteria include: lack of alternative treatment, disease severity (such as a likelihood of premature death), small patient populations (with no specific threshold defined), and indications of potential clinical improvement through the drug (PBAC Guidelines). The 'rule of rescue' becomes particularly pertinent when the PBAC would otherwise deny reimbursement based on comparative cost-effectiveness. In such cases, a recommendation in favour of

reimbursement might be favoured under the rule of rescue, irrespective of a high ICER. The PBAC Guidelines note that a listing of a second medicine to treat the medical condition, on a cost-minimisation basis, is not suited for this consideration, as it does not meet the first criteria.

England and Wales (NICE)

The Highly Specialised Technology Program in England and Wales (NICE) considers drugs for very rare conditions with topics identified by the National Institute for Health Research Innovation Observatory. They aim to notify the Department of Health and Social Care of key, new and emerging healthcare technologies that may need to be referred to NICE; new drugs in development, are referred at 20 months prior to marketing authorisation; and new indications, are referred at 15 months to marketing authorisation. The provisional evaluation topics are then chosen and manufacturers are invited to make a submission via the Highly Specialised Technologies pathway. A single highly specialised technology evaluation only covers a single technology for a single indication.

In decision-making, the committee considers that size of the incremental QALY gain in relation to the additional weight that would need to be assigned to the QALY benefits for the cost effectiveness of the technology to fall within the highly specialised technologies £100,000 cost per QALY level. The NICE Manual (2022) specifies that compelling evidence is needed that treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained. The QALY weighting applied to the size of benefit for highly specialised is provided in Table 23.

Table 23 Weighing according to the size of benefit for highly specialised technologies.

Incremental QALYs gained (per patient using lifetime horizon)	Weight
Less than or equal to 10	1
11 to 29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

QALY= quality adjusted life year.
Source: NICE Guidelines [3]

The NICE Guidelines (2022) does stipulate that it is not possible to set absolute timelines for all stages of the evaluation, which is dependent on the nature of particular evaluations, as well as particular stages that coincide with public holidays. Although, this statement in the NICE Manual is not specific for highly specialised technologies.

The NHS in England and Wales also have the Early Access to Medicines Scheme (EAMS) aims to give patients with life threatening or seriously debilitating conditions access to medicines that

do not yet have a marketing authorisation when there is a clear unmet medical need (UK Government) [193]. Under the scheme, the Medicines and Healthcare products Regulatory Agency (MHRA) will give a scientific opinion on the benefit/risk balance of the medicine, based on the data available when the EAMS submission was made. The opinion is granted for 1 year and can be renewed.

Scotland (SMC)

In June 2018, Scotland (SMC) introduced the 'ultra-orphan' pathway for medicines meeting specific criteria [44]. Through this pathway, medicines can be made available in Scotland for a period of three years prior to a decision on routine use in NHS Scotland. There are four key stages for medicines undergoing this pathway:

1. Validation (approximately eight weeks). During this stage the SMC review applications to ensure all criteria[7] is met for the medicine to progress through this pathway;
2. Initial SMC assessment (around 18 weeks). The initial assessment report is published within SMC's standard timelines. Sponsors make a full submission using the New Product Assessment Form (NPAF) for ultra-orphan medicines and must offer a Patient Access Scheme (PAS). The purpose of the PAS is to enable patient to receive access and improve cost-effectiveness of the medicines. Sponsors are encouraged to offer a fair price in return for flexibility offered though this pathway. The PAS will only become available for implementation if approved by the Patient Access Scheme Assessment Group (PASAG) (which is part of the NHS);
3. Evidence generation (up to three years). Sponsors are required to develop a data collection plan to address uncertainties with the existing evidence base, and as identified in the initial SMC assessment report. Data collection and all associated costs are the Sponsor's responsibility. Evidence generation can begin at an early stage in parallel with initial SMC assessment.
4. Reassessment (around 22 weeks). Sponsors are expected to submit an updated full submission to the SMC for reassessment following the three-year evidence generation stage. The SMC assess the updated full submission and other sources of evidence e.g., clinician experts, patient group submission, and output from a patient and clinician engagement (PACE) meeting. SMC decision options at reassessment are either

[7] All criteria must be met where the condition: 1) has a prevalence of 1 in 50,000 or less; 2) has EMA orphan designation which is maintained at time of marketing authorisation; 3) is chronic or severely debilitating; and 4) requires highly specialised management.

'accepted for use', 'accepted for restricted use', or 'not recommended'. If the SMC advice is 'not recommended' the sponsor can request to convene a Patient and Clinician Engagement (PACE) meeting (that adds an additional one to three months to the assessment timeline). This is an additional meeting of patient groups and clinicians to explore the value of the medicine, that may not be fully captured within the conventional clinical and economic assessments [45]. The output from PACE meeting is a major factor in the SMC decision.

The Ultra-Orphan Drug Risk Share (2020) provides funding for medicines approved via the ultra-orphan medicines pathway, and a small number of medicines for extremely rare conditions that have been accepted by SMC outside of that pathway (ref: NHS Scotland website, Ultra orphan medicines (published 31 August 2023) [182].

Additionally, the SMC guidelines state that for ultra-orphan indications, CCA can be presented as a supportive analysis, where multiple relevant outcomes are not captured in QALY [194]. A wider perspective than NHS perspective may also be considered.

Germany (IQWiG and G-BA)

In Germany (IQWiG and G-BA), added benefit is assumed to be proven for orphan drugs at the time of European approval for subsequent market access [195]. The HTA process for orphan drugs does not require an economic evaluation, if the annual turnover for the drug does not exceed €50 million [195]. This process for the special orphan drug assessment (i.e., limited assessment) was introduced in 2011. Orphan drugs not meeting the turnover criteria are processed through regular benefit assessment. IQWiG conducted a cross-sectional analysis of orphan drugs that were granted market access since 2011 [187]. In this analysis, 20 orphan drugs were identified for which a limited assessment and a regular benefit assessment have been conducted (total assessments, N=41). IQWiG found that in 22 (54%) assessments, no added benefit (i.e., not proven) could be determined through the regular benefit assessment. From the 22 assessments where added benefit were not proven, the classification of added benefit is usually only corrected after some years, where the period between the limited and the regular benefit assessment was on average three years (range: 1 to 9 years). In some cases, the classification of added benefit is not corrected, where the revenue threshold of €50 million is not exceeded for the orphan drug and a regular benefit assessment is therefore not conducted [187].

Belgium (KCE)

The HTA requirements indicate that a lower level of clinical data may be accepted for a conditional reimbursement approval, and real-world effectiveness data would be required after the approval. The submissions for reimbursement of rare disease need to contain at least efficacy data, budget impact analysis, and preferably evidence on the effectiveness [14].

France (HAS)

In 2021, the remit of HAS was extended to include responsibility for decisions made for early access authorisation for medicines and their public funding cover [185][8]. The HAS emphasises that prioritisation should be given to participation in ongoing clinical trials where the medicine is used over early access authorisation.

Early access authorisation is applicable for medicines where an indication for which marketing authorisation has not been granted yet by the French National Agency for Medicines and Health Products Safety (*Agence Nationale de Sécurité des Médicaments et des produits de santé* (ANSM)). The ANSM provide their review on the presumption of efficacy and safety of the indication. If considered favourable by the ANSM, the manufacturer can apply for an early access authorisation for a specific indication. The HAS makes a decision based on the eligibility criteria: medicinal products indicated for a severe, rare or incapacitating disease meeting eligibility criteria where: 1) there is no appropriate treatments; 2) the initiation of treatment cannot be deferred; 3) the efficacy and safety of the medicine are strongly presumed based on the results of clinical trials; and 4) the medicine is presumed to be innovative, compared with a clinically relevant comparator.

Early access authorisations are subject to the manufacturer complying with a protocol for temporary use and data collection, which is set out by the HAS in collaboration with the ANSM where applicable, and appended to the authorisation decision. The responsibility for the management and funding of the real-world data collected in the context of early access is not stated.

For medical devices, an application for temporary coverage can be made which allows for products to be reimbursed for one year, pending the conventional reimbursement process. This includes products and services used for the treatment of a serious or rare disease or to compensate disability. To be eligible for temporary coverage, products and services must meet

[8] The HAS state in the guide 'Authorisation for early access to medicinal products: HAS assessment doctrine' that the English version is published for information, however only the French version is deemed authentic.

conditions outlined in the decree[9]. Three prerequisites must be met: 1) It must have 'CE marking'[10] if it is a medical device; 2) the product must not already be reimbursed as part of hospitalisation services; and 3) the manufacturer must undertake to submit a request for inclusion on the list of products and services qualifying for reimbursement for the medical device within 12 months of the application for temporary coverage.

Canada (CADTH)

In 2018 and 2021, CADTH conducted a review of drugs for rare disease and their decision-making processes across national and international HTA agencies and public payers [196, 197]. This report included Canada (CADTH and INESSS (Quebec)), England and Wales (NICE), Scotland (SMC), France (HAS), Germany (IQWiG, G-BA), Australia (PBAC), New Zealand (PHARMAC) and US (ICER-US). The review noted that there were some variations across agencies in the submission process for these programs for drugs for rare disease in terms of whether they use the same submission forms and processes or separate ones. Some HTA agencies have established separate evaluation committees to evaluate drugs for rare disease, under their processes, and all of them consider patient input in their decision-making framework. Evaluations of drugs for rare disease are generally based on clinical and economic evidence, but most organisations do recognise the paucity of robust clinical and economic evidence, and that a simple "utilitarian" approach to these evaluations does not sufficiently recognise the unique needs of the rare diseases. Although economic evidence is considered by these HTA organisations and funding programs in their decision-making processes, most either make some consideration or do not consider economic evaluation a predominant factor in their decisions.

The CADTH review concluded that several drugs for rare diseases have been developed that have offered potentially effective therapies. The industry's shift in focus toward niche markets such as drugs for rare diseases is evident from the increase in the number of drugs for rare diseases in the pipeline and those being marketed. The expected yearly growth of drugs for rare disease is approximately 11%, which is more than twice that of conventional drugs on the market. The number of drugs for rare disease submissions to the CADTH Common Drug Review almost doubled between 2004 and 2015. There were four to five submissions for drugs for rare disease per year between 2004 and 2012, which increased to 10, nine, and eight in 2013, 2014, and 2015, respectively [196, 197].

[9] Document is in French, URL:
https://www.legifrance.gouv.fr/download/pdf?id=YfGYL2kkDMS2OWSxGbVjZVIsrsa00QFujiQScSI_fAU=
[10] The letters 'CE' appear on many products traded in the European economic area. The CE marking signifies that products sold in have been assessed to meet high safety, health, and environmental protection requirements.

Published peer-reviewed literature

Carr and Macaulay (2021) [198] reviewed medicines that have been reimbursed though the SMC ultra-orphan pathway (established since 2019) and compared reimbursement timelines and decisions with other HTA jurisdictions (including England and Wales, NICE; Germany, GBA; France; HAS). Four medicines were identified (Waylivra (Nov-2020), Brineura (Oct-2020), Luxturna (Feb 2020), Crysvita (Feb-2020) for comparison that were recommended by SMC, which had an average of 24.3 months post-European Commission approval, compared to a mean of 7.8 month approved by NICE via HST pathway. Although not reported in the abstract by Carr and Macaulay (2021), differences in timelines may be due to NICE allowing for a parallel process of registration and reimbursement processes, whereas the SMC conduct HTA evaluation after EMA registration is granted. However, the SMC do encourage sponsors to contact the SMA prior to EMA registration being granted.

Pearson et al [41] reviewed UK (England and Scotland) publications in relation to ultra-orphan submissions. The paper concluded that orphan drug products must undergo formal HTA, including economic evaluation, after regulatory approval to gain reimbursement in some European jurisdictions. Orphan drugs often have limited or weak clinical and safety data at product launch, and inadequately powered trials may contribute to uncertainty in the results of an economic model. Many orphan diseases are paediatric and/or may be associated with increased mortality rates, and trials in such diseases may be stopped early on ethical grounds. When there are limited or uncertain clinical data available, health economists may turn to other clinical data sources, such as patient registries and external clinical experts. However, associated challenges with patient registries are related to data ownership and limited comparator data.

Pearson et al [41] concluded that the traditional outputs for economic models, including QALYs and disability-adjusted life-years, may not be sensitive to the severity of rare diseases, and may not adequately reflect societal preferences for the treatment of life-limiting rare diseases. Although some HTA bodies may not consider traditional threshold values, such as cost per QALY gained, when evaluating a drug for a rare disease, HTA bodies often do consider the effect of the treatment on the quality of life of patients and patient caregivers. Where data are scarce, clinical opinion should be sought on the use of published data from a more prevalent but similar disease. For example, data on health care resource-use and quality-of-life from multiple sclerosis could be leveraged for rare diseases.

Nicod et al [199] used a mixed-methods design to document country appraisal/reimbursement processes for rare disease treatments and identify the features used in these "supplemental"

processes. The authors contacted experts in HTA processes for rare disease treatments in all European Member States and the European Economic Area, Canada and New Zealand, and invited them to participate in the research. 13/33 jurisdictions include supplemental processes specifically targeting rare and/or ultra-rare disease treatments. The main distinction between separate supplemental and standard processes is the different evidence submission requirements and appraisal committees.

Rare disease treatments are also subject to more simplified evidentiary requirements (e.g., no need for comparative data), and their additional benefit is considered automatically proven. There is also an option for conditional approval. Many jurisdictions include conditional approval agreements or MEAs, aiming to collect additional data to facilitate later re-assessment of added benefit or cost-effectiveness. Some jurisdictions also include alternative routes to pricing and reimbursement for a group of rare disease treatments.

Conclusion

Generating evidence for rare diseases poses challenges due to difficulties in recruiting patients for clinical trials. Despite higher levels of clinical uncertainty, the negative impact on HTA outcomes might be balanced by a stronger perception of unmet clinical need associated with rare disease [165].

Separate evaluation committees have been established in some jurisdictions, including Australia, to evaluate drugs for rare disease requiring treatment with an ultra-orphan drug. For all jurisdictions with established rare disease committees, consideration of patient input is factored into their decision-making framework. Evaluations for drugs for rare disease are generally based on clinical and economic evidence, but most HTA agencies/organisations do recognise the paucity of robust clinical and economic evidence. Although economic evidence is considered, there are differences with respect to consideration of economic evaluation being a predominant factor in their decisions.

For ultra-rare diseases, setting up patient registries could prove useful. These registries would house data about the natural history of the disease and baseline risks. This information would help contextualise the clinical effectiveness of treatments within the broader epidemiological context. HTA agencies could also play a role in designing patient registries to ensure that the data collected adequately assesses the effectiveness and cost-effectiveness of new drugs. The collection of real-world data in response to immature clinical evidence is also stressed in the literature [62]. Some jurisdictions include requests to gather supplementary registry data in

agreements to allow for reimbursement often on a conditional basis. These agreements may be referred to as Managed Entry Agreements (MEAs).

Why this matters?
A range of specific HTA pathways have been used to process treatments for ultra-rare and life-threatening conditions across jurisdictions. While many of these are similar in requirements (such as the need for generation of real-world evidence to ensure treatments are consistent with expected benefits) differences in process across the jurisdictions which can impact time to patient access. In Australia, the minimum time from submission to recommendation through the two committees, PBAC and LSDP, is approximately 38 to 42 weeks based on the procedure guidance [21, 43], and may be longer in practice. Treatments listed for LSDP are subject to a review for 24 months post listing to ensure usage is consistent with expected benefits and usage. In Scotland (SMC), patients can obtain earlier access though a Patient Access Scheme (PAS). Medicines are processed through the ultra-rare pathway, where after validation and initial assessments (~26 weeks), a PAS is conducted for the evidence generation phase (three-year period). Accountability for design, data collection, and report for the PAS is placed on the sponsor. The PAS will only become available for implementation if approved by the Patient Access Scheme Assessment Group (PASAG) (which is part of the NHS). Treatments must then undergo reassessment where applicants submit a full submission for SMC review. This process may include other evidence from patients and clinicians (PACE advice), which factors into final decision-making.

High unmet clinical need and equity considerations

High unmet clinical need

Unmet clinical need (also termed unmet medical need or unmet therapeutic need) is a concept that distinguishes between more urgent societal health needs from less urgent needs [200].

A 2019 scoping and grey literature review found 16 definitions of unmet clinical need that included one or more of the following elements: (adequacy of) available treatments, disease severity or burden and patient population size [201]. Other than the MSAC Guidelines, unmet clinical need was not explicitly addressed in any of the HTA guidelines reviewed. Unmet clinical need is often informally incorporated in HTA decision-making processes, with evidence of significant influence in approvals for orphan drugs [46]. England and Wales (NICE) formally incorporate unmet need through a severity or burden of illness modifier, which adds QALY weights and hence increases the cost-effectiveness threshold [50].

In Australia the PBAC and MSAC allows for flexibility in evidentiary requirements including for medicines used to treat less common and rare diseases with a high and unmet clinical need for new treatment options. The MSAC guidelines recommend that affected subgroups should be identified for health technologies that address health inequalities (e.g., those resulting from differences in access to care in rural and remote areas, or an area of unmet clinical need). The PBAC guidelines describe 'clinical need' as one of the less-readily quantifiable factors influencing PBAC decision making. Decisions made by the PBAC in areas of unmet clinical need can be recorded in public summary documents.

In contrast to most reimbursement bodies, many regulatory bodies incorporate unmet clinical need formally in assessing technologies. Unmet clinical need has become a criterion for technologies to be eligible for regulatory processes such as conditional marketing authorisation and accelerated assessment, including being used for prioritisation of eligible products within the European Medical Agency's Priority Medicines scheme [201]. This has implications for HTA processes as, relative to standard approval drugs, conditionally approved drugs are less likely to be based on phase III trial designs, clinical endpoints or an active comparator [165]. This leads to greater uncertainty in clinical and economic evidence, resulting in both delayed and reduced HTA approvals relative to drugs with standard approval [165].

Health equity

The objective underlying CEA is typically to provide information of the 'value for money' of the proposed technology (efficiency). However, such analyses do not provide information on who

benefits and who loses from the approval and reimbursement of new technologies (given that for a healthcare system with limited resources, introducing a new health technology system benefits some patients, but funding that technology displaces the opportunity to provide alternative technologies, leading to health losses for others (health opportunity cost)) [51]. As such, decision makers may inadvertently worsen health inequalities among certain population groups (defined socially, economically, demographically, or geographically) which may be deemed as unfair (equity) [202].

Assessing health equity in HTA

Of the international HTA guidelines reviewed, only five explicitly mention that equity implications of the technology are important and should be considered (Canada (CADTH); England and Wales (NICE); Korea (HIRA); Scotland (SMC); Taiwan (NIHTA)). In each case, consideration of equity occurs alongside CEA with all guidelines recommending equal weighting of QALYs for the base case analysis, regardless of the characteristics of people receiving, or affected by, the intervention in question. Three agencies (England and Wales (NICE); the Netherlands (ZIN); Norway (NIPH)) have operationalised the practice of applying equity weights to specific population subgroups as a means of increasing the cost-effectiveness threshold for some new health technologies [203]. In other jurisdictions, qualitative deliberation may be the method by which factors for equity are considered (see discussion in Part 1 –weighted scales).

The PBAC and MSAC guidelines state that decision-making is not solely determined by quantifiable impacts on health but are also informed by less-readily quantifiable factors including equity and are considered on a case-by-case basis [2, 72].

Vulnerable and disadvantaged populations

Australia and New Zealand, in light of higher burdens of disease and challenges in accessing health care services among Aboriginal & Torres Strait Islander and Maori populations respectively, have adopted special authority ethnicity criteria for some medications [47] [48]. New Zealand has also piloted an equity capability self-assessment tool with the Pharmacology and Therapeutics Advisory Committee (PTAC) [48].

Quantifying health equity impacts

Methods to quantify the equity impacts of health technologies, namely distributional cost-effectiveness analysis (DCEA) [49], have been explored in the literature but are yet to be implemented in practice. The feasibility of incorporating DCEA within HTA processes is currently

being explored by NICE (England and Wales) [50], however challenges arising from a lack of consistency in how equity concerns are defined and how data are collected and reported [51].

Conclusion

A limited number of HTA guidelines explicitly mention that health equity impacts are considered in decision-making, with qualitative deliberation the predominant method used, including in Australia (MSAC/PBAC). Despite much progress in recent years to advance the quantitative assessment of health equity impacts in HTA processes, this has yet to be implemented in practice and several challenges remain.

Why this matters?
Australia is one of few countries which explicitly state that unmet clinical need, vulnerable and disadvantaged populations and health equity are important considerations in decision-making processes for new health technologies. Unlike England and Wales (NICE), the lack of an explicit cost-effectiveness threshold in Australia allows for such factors to be considered qualitatively rather than quantitatively. Incorporating emerging quantitative methods, such as DCEA, could improve transparency in how such factors are weighted during the decision-making process. However, this is currently hampered by a lack of consistency in how equity concerns are defined and how data are reported and collected. Therefore governments and HTA agencies must be explicit about which equity concerns are of most interest and recommend or develop generic indices to best capture them.

Co-dependent technologies

Technologies are co-dependent when their combined use (sequentially or simultaneously) achieves or enhances the intended clinical effect of the technologies when used separately [72]. An example is the use of a companion diagnostic test alongside a cancer drug to identify patients who are most likely to respond to the treatment, thereby improving the effectiveness of the drug. Co-dependent technologies can also be referred to as 'companion diagnostics'.

The dynamic progression of clinical pathways, incorporating companion diagnostics, presents complexities in the design of clinical trials and the selection of comparators, which flow on to the conduct of the economic evaluations. Co-dependent technologies necessitate an HTA process that considers their interdependencies and collective impact i.e., clinical utility. Therefore, the net clinical benefits of the joint use of the technologies, as distinct from the net

clinical benefit of each technology used separately, needs to be determined. There are two approaches used to assess the evidence:

- Direct evidence: the clinical studies presented directly compare patients who receive either the current or the proposed diagnostic test. Evidence is typically from RCTs or observational studies. These studies evaluate the differential effect of the diagnostic method on patient health outcomes. If patients are randomly assigned to receive the test, their biomarker status is known, and subsequent treatment decisions can be based on that information. Conversely, if patients are randomly assigned to not receive the test, they would receive a treatment that is not influenced by the biomarker result.
- Linked evidence: test accuracy comparing the proposed and current test/test strategy is connected through different sources of evidence of diagnosis, treatment decisions, and outcomes in marker-positive and marker-negative populations, enabling the modelling of the benefits of the co-dependent technologies [204]. This method can facilitate the identification of uncertainties associated with the decision to use or not use the diagnostic, providing a framework for assessing clinical utility when RCTs are not feasible. The approach can also be useful if key evidence of clinical utility of the predictive biomarker is missing.

The use of different approaches has implications on the methodology and robustness of an economic evaluation as part of HTA.

Clinical trials of new interventions are often developed around unselected patients [205]. However, as co-dependent technologies become more sophisticated, companion diagnostic test can identify a wider range of factors influencing a patient's response to treatment. This means that mutation-specific tests, which focus on one particular genetic change, may become obsolete because they provide only a limited view of a patient's potential response to treatment.

Ideally, achieving reimbursement for both the pharmaceutical and its companion diagnostic, for example, is the preferred approach to ensure patient access within the public health system. However, there may be misalignments in the decision-making processes for these two components. This misalignment may stem from historically divergent pathways for reimbursement decision-making for medical devices and pharmaceuticals.

Comparisons of methods and processes across jurisdictions

A summary of the methods and processes used to evaluate co-dependent technologies discussed in the guidelines of the jurisdictions of reference is presented in Table 24. The subsequent sections provide detailed explanations of the methods and processes employed by relevant agencies, elaborating on their respective approaches. In the evaluation of co-dependent technologies, the methods employed do not significantly differ from those used for assessing single technologies. Key considerations such as effectiveness, cost-effectiveness, and safety remain crucial in both cases. However, there are distinctions in the evaluation process and evidence requirements for co-dependents as compared with single technologies.

Information on the processes and evidence accepted for co-dependent technologies were explicitly noted in the HTA guidelines of eight jurisdictions (Australia (PBAC, MSAC); England and Wales (NICE); Scotland (SMC); Canada (CADTH); France (HAS); Sweden (TLV); Belgium (RIZIV-INAMI); Singapore (ACE)).

Table 24 Co-dependent technologies across jurisdictions

Jurisdictions (Agencies)	Mentioned in guidelines	Type of process	Evidence required
Australia (PBAC, MSAC)	Yes	Joint	Analytical and clinical validity together with clinical utility and cost. Direct evidence preferred but linked evidence accepted
England and Wales (NICE)	Yes	Depending on their association with new or established drugs	Cost and accuracy and alternative tests. Direct evidence preferred but linked evidence accepted
Scotland (SMC)	Yes	Separate process. The diagnostics is assessed by the MPC and linked to SMC	Not specified
Canada (CADTH)	Yes	Joint	Analytical and clinical validity together with clinical utility and cost. Direct evidence preferred but linked evidence accepted
France (HAS)	Yes	Joint	Clinical utility, assessed in conjunction with the efficacy of the treatment in the same trial. Direct evidence required, linked evidence not accepted.
Sweden (TLV)	Yes for precision medicines and ATMPs	Not specified.	The value of a treatment-predictive test depends on how cost-effective the subsequent treatments are. The cost of the test must be included in the total treatment cost for the new drug. However, if the test is already being carried, and the information from the test can be used for choosing between a range of subsequent treatments, then the cost of the test need not be added to the cost for the new drug.
Belgium (RIZIV-INAMI)	Yes	Joint process since May 2019	Not specified

Jurisdictions (Agencies)	Mentioned in guidelines	Type of process	Evidence required
Singapore (ACE)	Yes	Joint, a co-dependent diagnostic technology, may be evaluated concurrently or in parallel with the ACE drug evaluation program.	Direct evidence preferred but linked evidence may be used, in the absence of direct evidence: (a) Evidence on diagnostic accuracy; (b) Evidence on impact of diagnostics on management decision; and (c) Evidence on the effectiveness of treatment as a result of diagnostics.

ACE= Agency for Care Effectiveness; ATMPs= advanced therapy medicinal products; CADTH= Canadian Agency for Drugs and Technologies in Health; HAS = French National Authority for Health; HTA= Health technology assessment; MPC= Molecular Pathology Consortium ; MSAC= Medical and Scientific Advisory Council; NICE= National Institute for Health and Care Excellence; PBAC= Pharmaceutical Benefits Advisory Committee; RIZIV-INAMI= National institute for sickness and disability insurance (Belgium); SMC= Scottish Medicines Consortium; TLV= Swedish Dental and Pharmaceutical Benefits Agency; UK= United Kingdom; There was no information pertaining to methods and processes for co-dependent technologies specified by these jurisdictions (Luxembourg; Spain; Japan; Norway; Korea; Taiwan and New Zealand).
Source: ACE guidelines 2023, C2H guidelines 2022, CADTH guidelines 2017, HAS guidelines 2020, INAMI-RIZIV guidelines, IQWiG guidelines 2022, MSAC guidelines 2021, NICE guidelines 2022, PBAC guidelines 2016, SMC guidelines 2022, TLV guidelines for precision medicine 2022 and ZIN guidelines 2016

Evidence requirements

The direct evidence approach was preferred by all of these jurisdictions; however, given challenges associated with the availability of direct evidence, the linked evidence approach is accepted by Australia (PBAC, MSAC), Canada (CADTH), England and Wales (NICE) and Singapore (ACE).

Two of the international agencies (England and Wales (NICE); France (HAS)) have explicit guidelines concerning the evidence required in the assessment of companion diagnostics. The HAS guidelines [206], stipulate that for a test to be considered a companion diagnostic, the predictive utility of the biomarker must be established or rely on robust assumptions, irrespective of whether the diagnostic is legally mandated. Otherwise, the test is categorised as a "conventional diagnostic". Germany (IQWiG) also requires the establishment of clinical utility for a predictive biomarker through an RCT involving both marker-positive and marker-negative patient populations receiving precision medicine [207].

A study conducted in 2017 [208] shed light on the limited availability of statistically significant evidence from RCTs for companion diagnostics among oncology drug approvals by the US FDA. Among the 35 oncology drug approvals examined, only 3 could provide such evidence, indicating the challenges in generating robust empirical data to support the use of companion diagnostics in clinical practice. The complexities associated with conducting RCTs for companion diagnostics, including ethical considerations, practical limitations, and other factors underscore the need for alternative approaches and considerations in assessing the effectiveness and clinical utility of co-dependent diagnostics.

Australia has adopted a pragmatic approach and allows applicants for co-dependent technologies to substantiate the linkage of different types of evidence (the linked evidence approach discussed above). This approach acknowledges the practical limitations that may impede the conduct of RCTs and offers a systematic methodology for assembling diverse types of evidence to establish the clinical utility and economic value for co-dependent technologies.

HTA process

Six jurisdictions have joint HTA processes in place for the evaluation of co-dependent technologies (Australia, PBAC and MSAC; England and Wales, NICE; Canada; France, HAS; Belgium, RIZIV-INAMI; Singapore, ACE). Sweden's (TLV) guidelines do reference the use of companion diagnostics in relation to precisions medicines and ATMPs however the HTA process undertaken in Sweden is unclear (p51-52 of the "Health-economic assessments and payment models for precision medicines and ATMPs"). Only the SMC in Scotland noted that the process for the review of diagnostics is referred to the Scottish Genomic Test Advisory Group (SG-TAG) or Scottish Pathology Network (SPaN), as appropriate, who advise SMC on the diagnostic testing aspects of the economic case. Belgium (RIZIV-INAMI) recently implemented a joint process in 2019, where it was considered that a desynchronised decision-making process hindered access for these technologies [207].

In terms of how co-dependent technologies are evaluated, there are a number of options in Australia. An MSAC co-dependent application is required if the co-dependent technologies include a medical service and diagnostic test ([52]). A PBAC co-dependent application is required if the co-dependent technologies include a combination of drugs [72]. An MSAC and PBAC co-dependent application is required where the co-dependent technologies include a diagnostic test (or consultative service) and a therapeutic drug not currently publicly reimbursed.

MSAC and PBAC co-dependent applications follow MSAC's PASC timeframes, and the final submission is considered by both MSAC and PBAC. A joint evaluation document is prepared and considered at a joint meeting of the PBAC's Economic Subcommittee and the MSAC's Evaluation Subcommittee. The full PBAC meets three weeks before the full MSAC, which aims to provide enough time for the PBAC to raise any questions if needed for MSAC consideration, and for the applicant to comment on the questions, and for the MSAC to consider its advice. Stakeholder submissions to the inquiry into approval process for new drugs and medical technologies in Australia (conducted over 2020 to 2021) [209] contended that gaps in the current system remain in the joint process used ([209] pp36-39). As submissions are considered in parallel or

jointly by the PBAC and the MSAC, it was argued that the process can result in longer times for the decisions being made [53, 209]. For example, as the MSAC's advice is not available prior to the PBAC's advice, this prompts an 'automatic' resubmission to PBAC. During the Inquiry, PBAC Chair, Professor Andrew Wilson indicated the PBAC's interest in exploring mechanisms that might provide greater flexibility in committee membership, noting that the PBAC already has a sizeable membership.

To date, most co-dependent technologies assessed in Australia have been drug or test combinations, where the new drug is seeking listing on the PBS and a related diagnostic test is required to refine patient selection and eligibility for the new high-cost drug. Hence the related test is simultaneously seeking listing on the MBS. There are two submission pathways for co-dependent technologies in Australia (Figure 7):

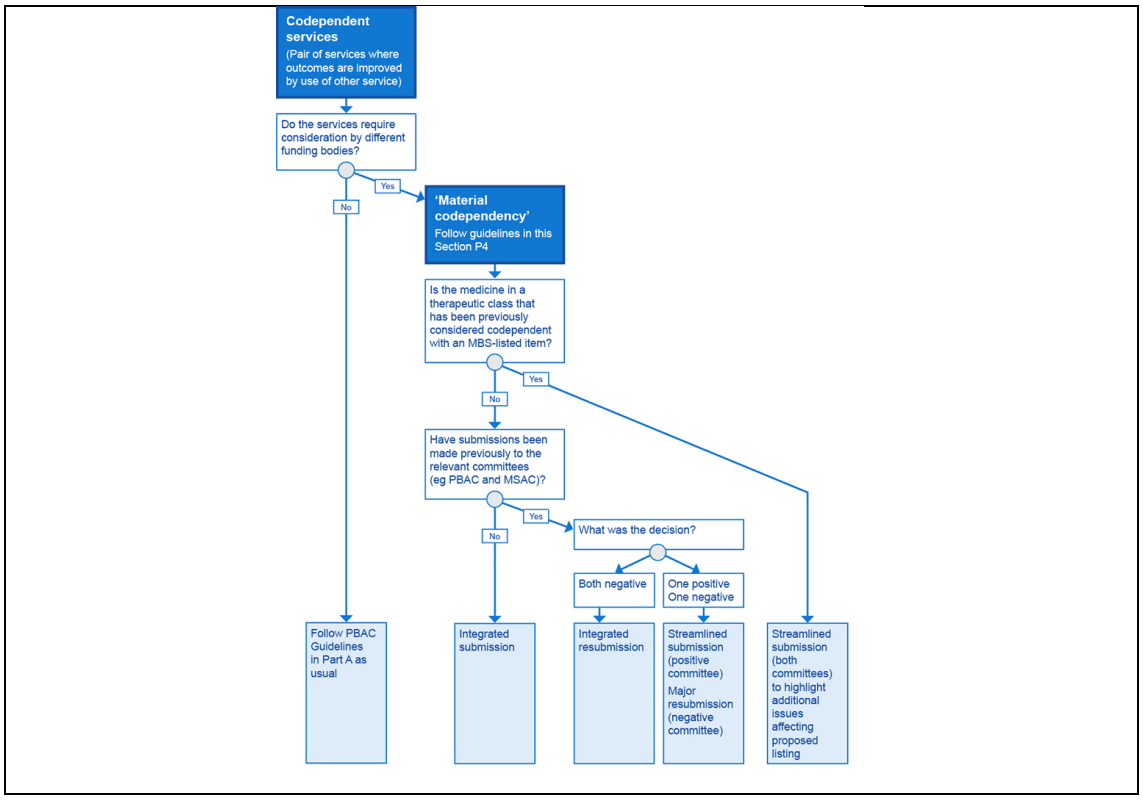
- Integrated co-dependent submission: A comprehensive submission encompassing both technologies is developed and evaluated collaboratively by the MSAC and PBAC. Integrated co-dependent submissions involve submitting a medicine to the PBAC along with a co-dependent test or investigative service that either requires listing in the MBS or joint consideration by both the PBAC and the MSAC for MBS listing. An integrated co-dependent submission is applicable when neither the test nor the medicine has been previously considered by either committee, when a resubmission is required based on the feedback from both committees, or when the medicine belongs to a different therapeutic class than a previously listed companion test.
- Streamlined co-dependent submissions: Separate submissions for each technology (one for the test and one for the medicine) are simultaneously lodged, allowing MSAC and the PBAC to independently review and assess the respective components in parallel. Streamlined co-dependent submissions are applicable when one committee has indicated support for the technology pairing after previous consideration, or if a minor amendment is needed for an MBS item descriptor to enable access to a co-dependent medicine in the same therapeutic class as a previously PBS-listed medicine, a streamlined co-dependent submission to amend the item descriptor can be lodged with MSAC alongside the submission to the PBAC for the co-dependent medicine.

Integrated co-dependent submissions often result in longer time to decision as the submission has to go to both committees (PBAC and MSAC). Parallel or streamlined co-dependent submissions, are lodged at the same time and follow the standard process outlined in the sections above. The pathway taken depends on several factors, such as, does the medicine

belong to a therapeutic class where co-dependency has previously been considered and whether a submission has been made to PBAC and MSAC previously [210]. MSAC appear to be receptive to making recommendations to create efficiencies in listings. In practice, MSAC try to create efficiency for pharmaceuticals relying on biomarkers, by broadening listings to classes of drugs rather than making listings specific for singular drugs. In other cases, other drugs may be added to the listings through a streamlined submission to make tests class specific.

One paper identified in the literature described the reimbursement pathways and processes for companion diagnostics for eight European counties (Belgium; The Netherlands; France; Switzerland; and Germany; UK, England; Spain; Italy) [207]. The authors explored whether legal timeframes were in place to finalise assessment and decision-making. For jurisdictions reporting approximate time frames (Belgium, England and Germany), the range varied from three months to three years (noting ranges in time were specified for each country). Govaerts et al (2020) [207] found that most jurisdictions did not have mandatory time limits in place and recommended alignment in decision-making processes for companion diagnostics and medicines.

Figure 7 Classification of integrated and streamlined co-dependent submissions



Source: PBAC Guidelines (Version 5.0)
MBS= Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PBAC= Pharmaceutical Benefits Advisory Committee. Note: In the situation where the medicine is listed but the test is not, a material co-dependency does not exist because the decision to list the test falls to MSAC alone.

Conclusion

The methods used for assessing co-dependent technologies show similarities to how other types of interventions are evaluated across all jurisdictions/agencies reviewed. When comparing international guidelines with the Australian PBAC/MSAC approach, we found consistency across agencies.

A key difference lies in the evidence needed, specifically for evaluating the clinical utility of diagnostic tests within co-dependent technologies. Australia's innovative linked evidence approach stands out, setting a new standard. This approach was later adopted by agencies like CADTH and NICE, showing its growing acceptance. The linked evidence approach has a significant benefit in accepting that evidence gaps exist, reducing reliance on RCTs needed for the direct evidence approach (i.e. HAS, France and IQWiG, Germany). This allows a broader scope of evaluation for co-dependent technologies.

Why this matters?
Applications for co-dependent technologies are reviewed by two committees as listing requires funding from two separate reimbursement schemes. Australia utilises a pragmatic approach for the assessment of co-dependent technologies, where the co-dependent technology is considered at a joint meeting of the PBAC's Economic Subcommittee and the MSAC's Evaluation Subcommittee. The application is then considered at two separate committee meetings (PBAC and MSAC). This facilitates for a comprehensive assessment; however, since PBAC advice is obtained prior to MSAC advice, this approach could potentially induce delays by prompting resubmission of applications to the PBAC. Facilitating MSAC advice prior to PBAC advice could potentially result in similar delays. Consolidating recommendations or advice under one of the committees, such as under the PBAC's authority may streamline the process. This would require cross-membership with MSAC to facilitate sharing of expertise.

New and emerging technologies

Many new complex therapies have emerged with a prominent focus on personalised health technologies, which may combine a growing number of technologies, including pharmaceuticals, devices, diagnostics, and digital tools. These new and emerging technologies represent medical advancements in personalised treatments and treatment pathways e.g., gene therapies, cell-based therapies, precision medicines, personalised medicine approaches, advanced biologics, and innovative medical devices. Precision medicine is an innovative

healthcare approach that considers an individual's genetics, environment, and lifestyle to guide medical decisions. In practical terms, precision medicine is a question of using molecular tests to identify which patients can be expected to benefit from a treatment. New and emerging health technologies discussed in this report are advanced therapeutic medicinal products (ATMPs) and histology-independent therapies. Some ATMPs may integrate medical devices (co-dependent technologies); this are known as combined ATMPs. These treatments potentially offer patients major health benefits including the potential for 'cure'.

ATMPs can be broadly categorised into three main types [211]:

1. Gene therapy medicines (e.g., voretigene neparvovec, Luxturna®): These therapies involve introducing genes into the body that can lead to therapeutic, prophylactic, or diagnostic genes into the body. These recombinant genes can be used for wide range of conditions in which there is a known genetic component.
2. Somatic-cell therapy medicines (e.g., CAR-T): This category encompasses therapies that utilise a patients' own cells or tissues and manipulate them to alter their biological characteristics. The modified cells may be employed for diagnostic, preventive, or curative purposes.
3. Tissue-engineered medicines (e.g., autologous chondrocyte implantation): treatment involves the use of modified cells or tissues engineered to repair, regenerate, or replace damaged human tissue used for treating injuries, tissue damage, and organ failure.

Histology independent interventions refer to medical treatments, therapies, or interventions that target a common mechanism or pathway across various histological subtypes. For example, in the context of cancer, histology independent interventions could refer to treatments that target a genetic mutation or signalling pathway that is present in multiple types of cancer, regardless of their specific histology.

For many of these ATMPs, initial estimates of clinical efficacy derived from shorter-term clinical trials are based on surrogate outcomes (e.g., proportion of patients with cell engraftment, or without tumour relapse). However, the benefits of these interventions are expected to be observed over a long period of time (usually the remaining lifetime of patients). The uncertainty generated by relying on short-term intermediate outcomes stems from the need to extrapolate these initial results to understand the long-term benefits expected over patients' lifetimes, and flow on to impact on the robustness of the conduct of economic evaluation. The high cost of therapies and diagnostics to identify eligible population, may require substantial upfront investment but may also generate long-term or lifetime health gains, which makes it unclear

which way the bias falls over a lifetime; making economic modelling likely to be sensitive to parameters such as assumed time horizon and discount rate. There are also ethical and social implications, as these therapies may raise questions about the safety, efficacy, and acceptability of modifying human cells and genes, as well as the equity and accessibility of these therapies for different patient groups [212] [213] [214].

Definition: Surrogate outcome

The term 'surrogate outcome' is used to refer to intermediate outcomes or biomarkers that are able to predict a treatment effect on a final outcome, and can substitute for the final outcome.

Surrogate outcomes play a critical role in this process as they provide a means of predicting long-term outcomes based on short-term data. However, the selection of surrogate outcomes must be justified and validated to ensure that they are accurate predictors of long-term outcomes. The term 'surrogate outcome' has been used interchangeably with other terms such as 'biomarker' and 'biological marker', leading to potential confusion regarding its definition. According to the Biomarkers Definitions Working Group[11] of the United States National Institutes of Health, a surrogate outcome must have two distinct characteristics [215], where the surrogate outcome:

- Is intended to substitute for a final outcome that is clinically relevant to patients; and
- Should predict clinical benefits based on scientific evidence.

Intermediate endpoints or biomarkers do not always predict changes in a final outcome. A surrogate outcome has the connotation of replacing the true (final) outcome in a clinical study by another outcome. Intermediate outcomes or biomarkers, on the other hand, are medical signs, characteristics and/or measurements or a set of measurements indicative of symptoms, health or general wellbeing of patients [215]. The definition of surrogate outcomes proposed by the Biomarkers Working Group has been adopted by regulatory agencies globally [216-219].

Comparisons of surrogate outcomes

An overview of the methods and processes used to assess the use of surrogate outcomes in economic evaluations discussed in the HTA guidelines is presented in Table 26. All agencies reviewed mentioned the use of surrogate outcomes in their HTA guidelines, however, only

11 The Biomarkers Definitions Working Group of the United States National Institutes of Health was formed in 1998 to address the need for clear and consistent definitions of biomarkers in biomedical research. The working group consisted of experts in the fields of laboratory medicine, clinical trials, and regulatory affairs tasked with developing a framework for defining biomarkers and establishing criteria for their validation and clinical use. The group has developed guidelines and definitions for the use of surrogate outcomes, important for ensuring consistency and clarity in the use of surrogate outcomes in clinical research and decision-making. Its recommendations have had a significant impact on the field of biomarker research and development.

Australia (MSAC), Australia (PBAC), UK (NICE), Canada (CADTH) and Singapore (ACE) provided guidance on the validation of the relationship from surrogate to final outcome.

Table 25 Methods use to assess the use of surrogate outcomes in economic evaluations

Jurisdiction (agency)	Mentioned in the guideline	Validation method
Australia (MSAC)	Yes	Outlined in Appendix 12 of the MSAC guidelines (Version 1.0 May 2021) validation of the surrogate outcome to estimate final outcomes. This process involves defining the surrogate outcome and the final outcome, establishing their biological link, presenting epidemiological evidence, and using randomised trial data to understand their treatment effect relationship. Ultimately, this process allows for the estimation of the comparative treatment effect on the final outcome based on changes in the surrogate outcome.
Australia (PBAC)	Yes	Four-step approach to validating the use of a surrogate endpoint to predict a final outcome: 1. Define the surrogate and the final outcome. 2. Biological reasoning for the link between the surrogate and the final outcome, including how pivotal the surrogate is to the causation pathway of the final outcome. 3. Present randomised trial evidence to support the nature of the surrogate to final outcome comparative treatment effect relationship. 4. Translate the comparative treatment effect on the surrogate from the randomised studies to an estimate of the comparative treatment effect for the final outcome.
England and Wales (NICE)	Yes	The uncertainty associated with the relationship between the end point and health related quality of life or survival should be explored and quantified. The bivariate meta-analytic method is suggested mentioning the bivariate meta-analytic methods and the TSD 20.
Scotland (SMC)	Yes	No specific method provided. However, it mentioned "accepted surrogate endpoints" with no definition of how to assess it. For orphan drugs, the guideline requires the relevance of surrogate markers and the theoretical basis for their selection are presented, which should then be related to quality-of-life data.
Canada (CADTH)	Yes	Validated surrogate outcomes are proven to be predictive of an important patient outcome. A surrogate outcome is valid only if there is a “strong, independent, consistent association” with an important patient outcome, and there is evidence from randomised trials showing improvement in the surrogate end point has consistently led to improvement in the target outcome.
New Zealand (PHARMAC)	Yes	No specific method provided
France (HAS)	Yes	No specific method outlined. "If the data required to measure life-years are not available, a survival prediction criterion may be used, but only if there is strong, established evidence of the predictive character of this surrogate endpoint. The correlation factor should be presented and duly justified. The uncertainty generated by the predictive relationship should be explored through a sensitivity analysis."
Germany [a] (IQWiG)	Yes	No ‘best’ method is defined, but correlation-based validation is the ‘preferred’ method, in the sense it has been most widely used in evaluations. Another option discussed is the surrogate threshold effect. A support document discusses threshold values reported in the literature, without enforcing them.
Norway (NoMA)	Yes	No specific method outlined, it mentions that a ‘documented causal relationship between the intermediate endpoints and the hard endpoints should be made available’ without references.
Sweden (TLV)	Yes	Not specified. However, the guidelines for precision medicines and ATMPs shows preference for SO that are causally linked to the hard outcome at the individual level (the treatment effect of an intervention over the final outcome comes from the treatment effect over the SO)

Jurisdiction (agency)	Mentioned in the guideline	Validation method
The Netherlands (ZIN)	Yes	A prerequisite for intermediate or surrogate outcome measures is a proven sensitivity to change in the clinical outcome. Another consideration is the analytic accuracy of the test with which the intermediate or surrogate outcome is measured. The EunetHTA guideline for surrogate outcomes is referenced.
Singapore [b] (ACE)	Yes	Reference the PBAC. Only present a surrogate outcome (that is not the primary outcome) when it is critical to the therapeutic conclusion or economic evaluation. Present any statistical associations (including the strength of the association and the precision) and include relevant statistical outputs (e.g., regression coefficients and R-squared) as an attachment. Present results of a meta-analysis for individual studies and provide any meta-regression outputs, the R-squared for trials, and the surrogate threshold effect.

ACE= Agency for Care Effectiveness; ATMPs= Advanced therapy medicinal products; CADTH= Canadian Agency for Drugs and Technologies in Health; EUnetHTA = European Network of Health Technology Assessment; HAS = French National Authority for Health; IQWiG = Institute for Quality and Efficiency in Health Care (Germany);MSAC= Medical and Scientific Advisory Council; NICE= National Institute for Health and Care Excellence; NoMA= Norwegian Medicines Agency; PBAC= Pharmaceutical Benefits Advisory Committee; PHARMAC= Pharmaceutical Management Agency ; SMC= Scottish Medicines Consortium; SO= Surrogate outcome; TLV= Swedish Dental and Pharmaceutical Benefits Agency; ZIN= The National Health Care Institute.
a A correlation of $R \geq 0.85$; $R2 \geq 0.72$ measured at the lower bound of the 95% percentage interval allows to conclude that the validation study represents a high reliable result. This interval $R < 0.85$; $R2 < 0.72$ to $R > 0.7$; $R2 > 0.49$ represents a medium reliable result between surrogate and patient-relevant endpoint. If a validation study shows high reliable results with statistically low correlation ($R \leq 0.7$; $R2 \leq 0.49$) measured at the lower bound of the confidence interval, then the surrogate is not considered as a valid endpoint"
b It is not necessary to describe the transformation of a surrogate to final outcome in detail if the SO has previously been accepted as valid by one of ACE's decision-making committees or an international HTA agency (e.g. PBAC, NICE or CADTH)
There was no information pertaining to methods and processes forco-dependent technologies specified by these jurisdictions (Belgium; Luxembourg; Spain; Japan; Korea; Taiwan).
Source: ACE guidelines 2023, CADTH guidelines 2017, HAS guidelines 2020, IQWiG guidelines 2022, MSAC guidelines 2021, NICE guidelines 2022, NoMA guidelines 2018, PBAC guidelines 2016, PHARMAC guidelines 2022, SMC guidelines 2022, TLV guidelines 2017, TLV guidelines for precision medicine 2022 and ZIN guidelines 2016.

All agencies providing methodological guidance about the validation of surrogate outcomes emphasised the importance of biological evidence to establish the surrogate to final outcome relationship. This includes noting that evidence of individual level surrogacy provided only by biological and epidemiological information should not be used to confirm correlation as there are multiple other factors influencing the treatment effect observed in the final outcome [220]. The methodological guidance found in the agency guidelines highlighted the importance of RCT evidence comparing different interventions to validate the relationship between treatment effect on both the surrogate and the final outcome.

Among the reviewed agencies, only IQWiG, provided a threshold for evaluating the validity of surrogate to final outcome relationships, measured in terms of the correlation coefficient (R^2), which is based on the correlation between treatment effects. Notably, the PBAC guidelines acknowledge the intricate nature of this assessment, recognising the absence of established quantitative techniques that establish a threshold of validity for a surrogate outcome [221]. Consequently, PBAC's approach towards appraising surrogate outcomes for use in economic evaluations leans more toward a qualitative framework. This is aligned with the literature [222] where it is recommended that the decision to employ surrogate outcomes for predicting clinical benefit should pivot on a nuanced balance of all factors affecting the surrogacy relationship

(epidemiological and randomised clinical trial evidence, biological reasoning supporting the relationship of surrogate and final outcome and the comparative treatment effect). This equilibrium weighs the potency of the surrogate relationship against the imperative of rendering judgments on new treatment effectiveness, surpassing mere correlation coefficients. Furthermore, the robustness of the surrogate relationship is mirrored in the span of the anticipated treatment effect on the final outcome. When correlation is lower, the interval widens, making evident the higher uncertainty surrounding the predictions.

Comparisons of methods and processes across jurisdictions

Two agencies (England and Wales, NICE; Sweden, TLV) are attempting to address the area of new and emerging technologies. In 2021, the TLV in Sweden, issued guidance on this topic (titled "Health-economic assessments and payment models for precision medicines") [54]. In July 2019, the NICE began a review of its evaluation methods, resulting in a report entitled "CHTE methods review. Developing the manual. Task and finish group report" published in August 2021[55]. An overview of the HTA guidance from these two agencies with respect to ATMP is presented below.

In addition, in the US, an early adopter of new technologies, the ICER-US has published adaptations to its value assessment framework (methodological guidelines for HTA) to accommodate potential cures and other treatments that qualify as "high-impact, single or short-term therapies" [223]. In summary, the updates proposed the use of cure proportion modelling for extrapolation (including common modelling approaches in sensitivity analysis) and threshold analyses for durability of effect (https://icer.org/).

The inquiry into approval processes for new drugs and novel medical technologies in Australia noted challenges facing the existing system providing 31 recommendations (see report [12]) [209]. Recommendations pertaining to cell and gene therapies and rare disease from the final report published from the inquiry included: recommendation 1) the creation of a Centre for Precision Medicine and Rare Disease within the Department of Health, to provide advice on research priorities, education and training for clinicians and patients, and the development of a comprehensive horizon scanning unit for new medicines and novel medical technologies; and recommendation 2) that a new pathway for cell and gene therapy be established to simplify the HTA processes. Implementation of these recommendations would require government investment to set up the centre and to meet these objectives as outlined by the inquiry.

[12] Report entitled: The New Frontier - Delivering better health for all Australians. November 2021. URL: https://www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Report

1. Sweden (TLV)

Additional value aspects of the treatment

The TLV concluded that the main obstacle to identifying the value of precision medicine and ATMP was the lack of evidence for how large the health benefits will be from various treatments and tests – compared to the alternative in the long term. To some extent, this means that there will be more certainty about the effect of a treatment. It also means that money is not spent on treatments for patients in cases where it will not be effective. Despite this, TLV does not currently consider HTA of precision medicine to be associated with less uncertainty than assessments of other types of drugs. The TLV also suggests that the assessment of ATMPs will not necessarily be related with an improvement in cost-effectiveness, despite the ability to identify patients who will not experience an effect in advance. This is because TLV considers that manufacturers are likely to adjust the pricing of the drugs to reflect the (improved) effect in the targeted patient group.

The clinical trials designed for ATMPs and histology independent interventions target specific molecular or genetic markers rather than traditional tissue-based categories based on the type of tissue in which they originate (for example, two patients with breast cancer may have very different genetic profiles, even though they both have the same type of cancer). Comparators are usually chosen based on the tissue type of the disease, therefore, trials for these technologies frequently encounter a challenge in terms of identifying relevant comparators. The TLV argues that it will often be reasonable to make separate calculations for different subgroups of patients based on tissue or type of diseases, particularly, when data, such as information on the relevant comparator and survival estimates, is available for those subgroups of patients. However, there will often be cases where effectiveness data is not available for different subgroups, which makes it harder to vary the effectiveness parameter in a well-informed manner in the simulations.

How uncertainty is reflected in the result of economic evaluations

When TLV conducts HTA, all available information about the long-term health benefits of a new drug is used. In addition, results from clinical trials, which is likely based on medical and biological considerations, are also taken into consideration. For ATMP in particular, situations of genuine uncertainty will arise, i.e., there is limited knowledge of the long-term outcome. If payment for these one-off treatments is made in full at the time of treatment and the actual long-term health benefit for the patient is not as large as expected, the cost may not be justified by the actual health gain (the resulting ICER is much higher than anticipated, indicating poorer

value). Current ATMPs therefore represent a greater risk to the payer than standard, chronic pharmaceutical treatment.

The TLV notes that not all uncertainty associated with ATMPs and their cost-effectiveness is unidirectional, hence not all possible deviations in clinical practice result in a higher ICER. Therefore, it is rarely reasonable to assume a lifelong effect. The TLV concludes that it is generally not reasonable to assume lifelong effects because this assumption only introduces uncertainty that tilts towards higher costs. Instead, they suggest using assumptions that consider a range of possibilities in clinical practice, ensuring a more balanced and realistic assessment of the technology's cost-effectiveness. It is also important that the health economic evaluation reflects the possibility of different outcomes. In the guidelines, the TLV described several methods for how this can be achieved:

- Present a base case scenario consisting of a probability-weighted average of different calculations of cost per health benefit (QALY), where each calculation reflects one possible outcome. For example, instead of having a base case scenario based on a fixed duration of the treatment effect, the base case can be calculated as a probability-weighted average of different ICERs, where the duration of treatment effect varies. These probabilities can then be standardised to a certain extent in order to create transparency and facilitate consistent assessments, i.e. that equals are treated equally. Using this method, the calculation better reflects the genuine uncertainty that exists as well as the possibility of different outcomes.
- Apply a higher discount rate to deal with situations of major uncertainty. However, TLV considers this to be an imprecise method for dealing with uncertainty.
- Implement new types of payment models such as outcome-based payment models and contractual arrangements for ATMP. The TLV suggests that outcome-based payment models with staggered payment and long follow-up have the potential to address several of the challenges associated with one-off treatments.
- Wait for a number of years before subsidising or recommending a treatment until better evidence is available; the TLV intends to develop a measure to quantify patient health loss from waiting for treatment.
- One possibility for the paying party and/or decision-maker in the face of great uncertainty over for instance health benefits, is to wait for a number of years before subsidising or recommending a treatment until better evidence is available. However, the consequences of waiting for treatment differ between diseases. Consideration

should therefore be given as to whether the long-term health effects to patients from postponing treatment should play a role in how much uncertainty is accepted, i.e. that more uncertainty is accepted if the condition is such that patient health would seriously and permanently deteriorate in an irreversible way if treatment were to be postponed. TLV therefore intends to continue the investigation into this idea, as well as to develop a measure to quantify patient health loss from waiting for treatment.

2. Methods proposed to update the NICE, UK methodological framework.

The rise of new regenerative medicines and cell therapies prompted a comprehensive investigation into how well NICE's evaluation processes aligned with these pioneering treatments. In particular, the review of methods focused on ATMPs and histology independent interventions. This effort aimed to ensure that NICE's methods to evaluate new health technologies stay up-to-date and adaptable [224].

In July 2019, the NICE began a review of its evaluation methods in a two stage consultation. The review culminated with the publication of the "CHTE methods review Developing the manual Task and finish group report" in August 2021 [224], and the current methodological guidelines published in in January 2022 [3].

Proposed changes to UK methodological framework to deal with challenging interventions.

The CHTE methods review report [224] put forward a series of refinements to the evaluation framework to deal with HTA for challenging technologies, in particular ATMPs and histology-independent treatments:

- ATMPs
    - Trial Design and Evidence Quality: The proposed changes underscore the significance of well-designed comparative clinical trials for ATMPs. The emphasis is on using validated clinical endpoints over a sufficient period of time (which was not defined in the document) to accurately assess clinical effectiveness against standard care. The need to minimise avoidable uncertainty through high-quality trial design is highlighted.
    - External Comparison Biases: Biases associated with deriving relative effectiveness estimates from external comparisons are acknowledged. The report emphasises the importance of identifying, documenting, and addressing such biases in NICE submissions.

- Subpopulation Analysis: The proposal suggests that ATMP manufacturers should assess clinical and cost-effectiveness in relevant subpopulations to enhance generalisability and mitigate the risk of health inequalities.
- Long-Term Effectiveness: The report proposed a robust justification of assumptions and extrapolations concerning long-term effectiveness. This includes evidence from (preferably comparative) trials with validated clinical endpoints.
- Scenario Analysis: Evaluations involving uncertainty about long-term benefits should include scenario analyses to explore the impact of different assumptions about long-term benefits.
- Cure-Proportion modelling: The report proposes considering cure-proportion modelling[13] as an option to support cure claims, provided assumptions about curative properties are substantiated by appropriate long-term clinical evidence.
- Net Health Benefits: The potential value of net health benefits approaches in presenting uncertainty is highlighted.

- Histology independent treatments
  - Controlled Clinical Trials: The report stresses the importance of controlled clinical trials to assess the prognostic and predictive value of biomarkers. The mere expression of a biomarker by a tumour is not sufficient to assume treatment efficacy.
  - Basket Trials: When basket trials are used, they should be properly designed and analysed. Internal comparators, random allocation of treatments, validated clinical endpoints, and inclusion of all relevant cancer types are recommended. Any deviation from these standards should be justified.
  - External Comparisons and Real-World Evidence (RWE): While external comparisons and RWE are noted as potential options. However, the report mentions that “some studies have established that estimates of relative effectiveness derived from an external comparison are biased and systematically favour the new intervention”; and that constructing comparator

[13] Cure proportion modelling, as discussed in the CHTE methods review report, is an approach used in HTA that doesn't require assuming a complete cure for all patients but rather considers that a proportion of patients may experience outcomes or trajectories different from the rest of the population in the trial.

groups using RWE[14] would require a robust methodological basis, which was not available at time of the development of the report. Therefore, well-designed comparative trials are preferred.

  - Heterogeneity: The report acknowledges the challenge of heterogeneity in histology-independent indications. Committees should carefully consider generalisability, subgroup analyses, and the impact of including or excluding specific subpopulations.

- General Considerations:
  - Discounting: The report highlights the potential impact of discount rates on ICERs for ATMPs. While there are no specific exceptions for ATMPs, the underlying principles of time preference and wealth effect should be appropriately applied.
  - Subgroup Analysis: The report emphasises the importance of justifying subgroup analyses and recommends defining subgroups at the scoping stage when possible.

The suggestions resulting from the evaluation were presented to a committee of NICE for consideration, leading to the incorporation of select proposals. Subsequently, certain recommendations were adopted into the final guidelines, while others were not. A summary of these, indicating their inclusion or exclusion, is presented in Table 26.

Table 26 NICE, England and Wales: proposal of modification of methods about challenging technologies

Proposal at first consultation stage ("case for change")	Change or comments on proposal at second consultation stage ("proposals for change")	Changed at second round? (draft manual)	Included in final manual
Medical technologies evaluations should now consider, when relevant, unpublished evidence and post-marketing surveillance data.	No comment	Unchanged	Yes, unchanged
Evaluations in which there is uncertainty about long-term health benefits should include scenario analyses that explore the effects of different assumptions about long-term benefits. This might include threshold analysis for the duration of treatment effects.	Implement proposal	Details added	Yes, details added

[14] RWE is employed to construct an external comparator by harnessing real-world data sources such as electronic health records and patient registries. The process involves selecting a real-world cohort that closely mirrors the characteristics of the study population in a clinical trial. Researchers then conduct comparative analyses to assess treatment outcomes, safety, and effectiveness in this real-world cohort in comparison to the trial group.

Proposal at first consultation stage ("case for change")	Change or comments on proposal at second consultation stage ("proposals for change")	Changed at second round? (draft manual)	Included in final manual
Cure-proportion modelling should be considered as an option.	Cure-proportion modelling could be considered to explore the trajectories of different subpopulations without necessarily assuming a 'cure'. Curative assumptions should be supported by appropriate long-term clinical evidence.	Changed, but omitted from manual	No
For evaluations including significant service delivery effects, NICE should seek information from relevant health and care system partners.	No comment	Withdrawn	No
When basket trials are used, they should be appropriately designed and analysed and include assessment of heterogeneity and allow borrowing between baskets.	When basket trials are used, they should include relevant internal comparators, use a random allocation of treatments, use appropriate clinical endpoints (with a validated relationship with the overall survival and quality of life of the patients) and enrol all patient groups relevant to the indication. Any deviations from this standard should be justified.	Changed	Yes, changed
When clinical trials do not include a comparator group, several methods to derive comparative evidence should be explored.	No comment	Withdrawn	No
When heterogeneity between groups within a population is a concern, any assumptions about homogeneity or heterogeneity and generalisability to clinical practice must be clearly presented, tested and fully explored.	Assumptions about homogeneity, heterogeneity and generalisability of subgroups to clinical practice must be clearly presented, tested and fully explored. Bayesian hierarchical models can be used in this context.	Details added, but omitted from manual	No
NICE should improve its processes for active horizon scanning for potential methodological and implementation challenges associated with emerging technologies and innovations.	No comment	Not mentioned	No. Work ongoing

NICE = National Institute for Health and Care Excellence (England and Wales); UK =United Kingdom.
Source: extract of Appendix Table 1, supplementary material, Angelis et.al. 2023.

The methods proposed in the CHTE methods review report described in Table 26 are not explicitly adopted in Australia, however, the PBAC and MSAC guidelines do not preclude a sponsor to submit applications using these methods.

A notable finding in the suggested modifications to NICE's methodology involves the use of model-averaging strategies to address uncertainty of different scenarios of a decision problem. This concept, similar to the one proposed by Sweden (TLV), entails constructing alternative models with varying structural assumptions that represent different judgment perspectives. The outcomes of these models are then combined through averaging, with their weights determined based on their reliability or credibility. These weights can be uniform or vary, established using ranking techniques resembling those employed in model selection, or derived through expert input methods. In Bayesian model averaging [225], the posterior distribution of a parameter is estimated, while non-Bayesian approaches determine the average outcome of all potential models, weighted by the likelihood that specific model specifications are correct (Sweden (TLV)). However, the proposal concludes that further development of the methods for model averaging is needed and does not endorse any specific approach.

Published peer-reviewed literature

A number of papers have reviewed HTA processes and methods pertaining to new and emerging health technologies. These are discussed below.

<u>Reliance on immature survival and use of surrogate outcomes</u>

The practice of extrapolating survival curves from limited-duration clinical trials has gained prominence within these complex therapies, often based on cure mixture models, ignoring the potential of surrogate relationships, and extrapolating heavily censored progression free survival (PFS) and overall survival (OS) data. However, these models assume a cure fraction that may not be justified by the trial duration, which is usually one or two years. Consequently, in this context, it is critical to assess the feasibility of both the existence and extent of a curative fraction. Rigorous and extensive scenario and sensitivity analyses are of great importance, as the curative fraction greatly influence the results of cost-effectiveness analyses [214].

Extrapolating highly immature and heavily censored PFS and OS data is subject of substantial uncertainty, hence this may not represent the preferred approach to estimate the long-term effect of ATMPs or histology independent interventions. A recent review was conducted of the literature, funded by the NIHR to inform future NICE policy on how to appraise cancer drugs with histology independent indications [226]. The review concluded "that it might still be preferable for NICE appraisals to adopt a surrogate-based modelling approach informed by predictions from meta-analyses which capture all relevant uncertainty, rather than to ignore potential surrogate relationships and extrapolate heavily censored PFS and OS data" "(Chapter 4, p43). The use of surrogate outcomes to inform economic evaluations is discussed before in

this section. Regarding the use of extrapolation for ATMPs and histology independent treatments the NIHR report found that:

- In the application of PSM, the extrapolation of PFS and OS occurs independently, thus informing the temporal evolution of distinct health states. However, challenges arise in the context of histology-independent interventions due to increased heterogeneity in the overall population, potentially necessitating the adoption of flexible parametric models, mixture models, or response-based models.
- Flexible parametric models, incorporating splines to model time's effect on the hazard function, offer enhanced flexibility compared to conventional parametric models. Nevertheless, these models may fall short in accurately projecting PFS and OS when heterogeneity stems primarily from differences in the natural history of various tumour sites. Furthermore, these approaches tend to extrapolate survival data using the final segment of the curve, introducing uncertainties in survival projections.
- Incorporating multiple subsets of patients into parametric mixture models addresses heterogeneity by using different distributions. While this approach may better capture between-tumour heterogeneity of patients, challenges persist in determining appropriate mixture counts and ensuring the plausibility of projected long-term hazards.
- Response-based landmark models condition survival modelling on predefined response evaluation time points. By differentiating between responders and non-responders, this approach can account for heterogeneity in outcomes, including HRQoL, and costs. Nevertheless, challenges emerge in determining an optimal landmark time point and managing uncertainty.
- Incorporating a Bayesian hierarchical modelling (BHM) framework offers potential to address heterogeneity by providing assessments for each tumour type while accommodating potential differences in treatment effects. Nonetheless, the immaturity of survival data and issues with model validation and population shifts pose challenges.

<u>Uncertainty</u>

When the long-term effect is entirely unknown, traditional methods for quantifying uncertainty, such as probabilistic analysis, are of limited use. Alternative approaches could include more frequent use of scenario analysis, as proposed by Huygens et al [227], particularly focusing on retreatment, waning of efficacy, and disease progression, , or a more frequent use of managed entry agreements based on outcomes, as proposed by Drummond et al [214, 228][214,

228][207, 221][207, 221][206, 220][206, 220][206, 220][206, 220][206, 220][206, 220][205, 219][204, 218][202, 216][214, 228].

Joint collaboration of HTAs

Cross-agency collaborations spanning multiple nations have been established with the primary aim of investigating complex medical interventions. These collaborations collectively engage in a spectrum of HTA activities, related to market access and reimbursement. In particular, agencies collaborate on prospective scanning of emerging trends, comprehensive evaluations of health technologies, negotiation of pricing arrangements, procurement procedures, and the exchange of pertinent information.

One initiative identified in the literature search addressing these challenges is the "Health Technology Exchange" (HTx) introduced by the European Union, which seeks to establish a comprehensive framework for Next Generation of HTA [229]. The HTx is a collaboration consortium with the European Network for HTA (EUnetHTA) and its stakeholders to pilot the implementation of HTA methods in Europe. Among their objectives the 'HTx will facilitate the development of methodologies to deliver more customised information on the effectiveness and cost-effectiveness of complex and personalised combinations of health technologies.' This initiative from the European Union has identified complex therapies challenging the current HTA process[15].

A noteworthy example of these collaborative efforts involves FiNoSe[16], which conducted a collaborative assessment of the health technology associated with betibeglogene autotemcel gene therapy (for transfusion-dependent β-thalassaemia) in 2019. Similarly, BeNeLuxA[17] participated in a joint appraisal of the health technology linked to onasemnogene abeparvovec for the treatment of spinal muscular atrophy in 2021. These instances serve as illustrative examples of resource and expertise pooling among nations, which might yield adaptable

15 ATMPs (advanced therapy medicinal products), companion diagnostic, advanced surgical interventions, combination of therapies, digital technologies, gene sequencing, histology-independent treatments, medical devices or wearable, orphan therapies, personalized treatments, preventive treatment or vaccine, proton, photon or laser therapy and therapy sequences.

16 FiNoSe is a HTA collaboration network between Fimea (Finland), NoMA (Norway) and TLV (Sweden). In practice, the co-operation means that the three agencies will write joint assessment reports for pharmaceutical products that contain both relative clinical and health economic assessments.

17 The Beneluxa HTA initiative undertake joint assessments of pharmaceuticals products following an application by a manufacturer for reimbursement. Although the members have conduct the assessment in the individual countries (Austria, Belgium, Ireland and the Netherlands), the agencies are committed to align timelines, methodology and content of HTA.

methodologies for the evaluation complex therapies and the formulation of financial frameworks [62].

Continuous HTA

In France, reimbursement decisions for ATMPs have been approached with caution due to uncertainties surrounding their long-term efficacy and safety [230]. To address these uncertainties, a coverage with evidence development strategy has been implemented. This involves conducting health technology reassessments based on additional cohort data gathered from all patients receiving the ATMP in France.

For example, in the case of axicabtagene ciloleucel (for the treatment of treatment of large B-cell lymphoma) and tisagenlecleucel (for the treatment of B-cell acute lymphoblastic leukaemia), specific key outcomes such as survival, remission status, disease progression, and adverse events are collected at various intervals after injection. These intervals include 28 days, 100 days, 6 months, and every subsequent 6 months. Hospitals report this data on a quarterly basis. To facilitate data collection, the Lymphoma Academic Research Organisation (LYSARC) data platform in France plays a crucial role.

For betibeglogene autotemcel, a similar approach is adopted, but with a reassessment period of up to three years. The data collected in a registry includes patient characteristics, treatment effectiveness (with a particular focus on its sustainability of effect), iron overload, and any organ complications. This long-term data monitors the therapy's efficacy and safety over an extended period. The HAS (France) also emphasised the importance of collaborating with the French registry of thalassemia patients to ensure comprehensive and meaningful data collection efforts.

A similar approach was adopted in:

- Germany [230], where at least four gene therapies have undergone HTA, resulting in reimbursement subject to coverage with evidence development. The G-BA required sponsors of those medicines to collect and submit additional cohort data to inform future reassessments.
- UK, NICE, through the Cancer Drugs Fund: reimbursement for axicabtagene ciloleucel [231] and tisagenlecleucel [232], were subject to collection of a combination of long-term follow-up data from the clinical studies with cohort data from UK treated patients in clinical practice to allow the reassessment to more robustly establish the long-term efficacy (through the trial follow-up data) as well as the (short-term) real-world effectiveness in the English setting.

Overall, the coverage with evidence development approach adopted in France, UK and Germany aims to strike a balance between providing access to these innovative therapies and dealing with the uncertainty in the long-term by ensuring continuous monitoring and evaluation of their long-term impact.

Use of single arm trials in economic evaluation

In precision medicine, basket trials have become a common approach to evaluate targeted therapies that address rare genetic alterations present in various tumour sites across heterogeneous patient populations. Basket trials are typically used to investigate experimental treatments and refer to designs where targeted therapy is evaluated in multiple diseases that have a common molecular alternation. These trials are often exploratory and/or non-randomised in design. Due to the low incidence of these molecular alterations, data from these trials often face challenges related to their immaturity and small sample sizes. Based on current HTA methods, uncertainties arise pertaining the prognostic impact of the genetic alteration due to the lack of data on existing treatment performance to further complicate matters.

One of the primary difficulties in estimating the effectiveness and cost-effectiveness of these tumour-agnostic therapies lies in establishing the counterfactual or the expected outcomes for patients had they not received the investigational therapy. To address these challenges, several approaches have been described in the literature:

- Direct Comparison with a Literature-Based Cohort: This involves comparing the outcomes of the intervention group in the basket trial with data from previously published literature on similar patients [233].
- Intracohort Comparison (ICC): In this method, subsets of patients within the intervention group, who may have received different prior treatments or dosages, are compared to provide insights into treatment effectiveness [234].
- Non-responder Control: This approach compares the outcomes of the responder patients in the intervention group with non-responders or patients who did not receive the investigational therapy [235].
- Triangulation approach: This method involves combining results obtained from multiple estimation methods to create a composite view of total uncertainty and achieve a more consistent estimation of the cost-effectiveness of the tumour-agnostic intervention compared to relying on a single method alone [236].

When direct comparative data is unavailable, the methods mentioned above can be employed to estimate a counterfactual, each having its strengths and limitations.

Conclusion

The review of international guidelines shows a progression toward integrating new evaluation methods for emerging technologies, notably, the methodologies proposed by the TLV and NICE . The PBAC and MSAC guidelines currently do not outline methods that address recent challenges of new and emerging technologies. The HTA methods discussed in this section and used by international agencies (such as cure-modelling, modelling averaging or the use of RWE in the construction of external comparator for basket trials) is not contained in the PBAC and MSAC guidelines. Subject to the emerging experience from the use of those international guidelines, it may be appropriate to adapt the existing Australian guidelines to incorporate methods specific to the evaluation of specialised technologies.

In the context of limited knowledge of long-term outcomes, the use of surrogate outcomes is an important factor traditionally used to inform reimbursement decisions, and is of considerable importance for new and emerging technologies given claims of cure with treatment. Surrogate outcomes provide valuable insight into potential treatment effects, guiding evaluations when extended outcome data is still immature. The review of international guidelines showed alignment of Australian guidelines with globally acknowledged methods for validating the application of surrogate outcomes in economic evaluations.

Why this matters?
All HTA jurisdictions are facing the challenge of new and emerging technologies to treat rare or complex conditions. Assessment of these technologies requires methodological considerations that are not specifically covered by general PBAC and MSAC guidelines. While general guidelines provide a starting framework and flexibility of evaluation in terms of methods, they may not adequately capture the nuances and evidentiary challenges of assessing new and emerging technologies. Two agencies have commenced work leading HTA methodology for these technologies. The TLV and NICE, have both published guidelines for the consideration of methods applicable for new and emerging technologies. Subject to the emerging experience from the use of those guidelines, it may be appropriate to adapt the existing Australian guidelines to incorporate methods specific to the evaluation of specialised technologies.

Separate or combined consideration of multiple small populations/sub-groups, and flow-on effects for pricing.

Clinical benefit may vary by subgroup for treatments receiving regulatory approval for multiple-indications. The development of agnostic therapies (e.g., histology independent interventions, immunotherapies and targeted drugs) has rapidly evolved, where regulatory approval may be granted on the basis of basket trials or single-arm studies. Also in this space are other drugs, which have multiple indications, which may have been approved in quick succession where extension to indications is granted; notwithstanding the varying degrees of clinical benefit across the patient populations e.g., cystic fibrosis transmembrane conductance regulator modulators. The appropriateness of setting prices by indication to reflect differences in value is subject to debate.

Comparisons of methods and processes across jurisdictions

HTA is typically conducted for a single-indication at a time (Australia, PBAC; UK, NICE; Scotland, SMC), or in the event of a sponsor applying for multiple indications at the same time, the evidence supporting the listing in each population is typically considered separately. Accordingly, there is limited guidance provided in HTA agency websites on the combined consideration of small populations/subgroups, and from this respect, it is difficult to ascertain the methods currently being used for pricing pertaining to multiple small populations and subgroups. For this reason, information pertaining to this topic is informed by the literature.

Methodologies for flow on pricing from the literature

A number of papers have been reviewed regarding flow on pricing for separate or combined considerations of small populations/subgroups. Three pricing methods described in the literature are [59, 60]:

- Single price policy i.e., "single (lowest) price mechanisms" with "one price for one drug": Under a single price policy, manufacturers may be incentivised to prioritise, delay, withhold, or brand certain indications in order to achieve the highest possible price and profit. Based on this, the indication with high clinical benefit and strong evidence with a small patient population is launched first. The small population means there is a low impact on healthcare budgets. Subsequent submissions seek to expand reimbursed access to larger patient populations, albeit those may be associated with lower clinical benefit or weaker clinical evidence. Uniform pricing could have a negative impact on access, since some lower-value indications may not be reimbursed. In addition, uniform pricing could discourage the development of additional high-value indications if the uniform price is based on a low-value indication. However, the return to the manufacturer is based on both the price and the total volume of sales. A single price policy may lead to a higher cost to government, where price is based on the initial indication being launched, evidence is strong evidence and the clinical benefit is high.
- 'Indication-based pricing' (also known as indication-specific pricing or multi-indication pricing). This method applies a differential price according to benefit or value delivered for each indication. Theoretically, indication-based pricing could improve social welfare in the sense that more patients could access treatment, regardless of surplus distribution between consumer and producer. This method of price discrimination may enable prices to be set to the maximum WTP for each indication.
- 'Indirect indication-based pricing' methods, which is described as differential discount, weighted-average prices, clinical restrictions, and use of financial and outcome based managed entry agreements. Price may be weighted by expected use, indication, or other factors. This method appears to maintain discretion in pricing, particularly through the use of executed agreements.

Campillo-Artero et al [59] conducted a systematic review (January 2000 to September 2018) to examine the advantages and disadvantages of indication-based pricing practices. The authors found that the most prevalent approach is a single list price for a given drug, which may or may not be set on the basis of weighting across multiple indications. They also found a pure

'indication-based pricing' approach is not applied across Australia, the US, or in European jurisdictions, rather that 'indirect indication-based pricing' methods where agreements with regional buyers, insurers and hospitals, which are generally confidential and linked in most cases to risk-sharing agreements is a commonly used approach.

Michaeli et al [60] examined methods for pricing and managing costs for 25 multi-indication oncology treatments across 100 indications. In this study, the authors included coverage decisions made in the US, Germany, France, England, Canada, Australia, and Scotland. Data were extracted from HTA reports from agency websites for each drug and indication. Information on recommendations, disease prevalence, and drug prices were obtained. QALYs gained, disease prevalence, list prices, and HTA outcomes were then compared across indications and jurisdictions. The authors found that indications initially approved provide a higher clinical benefit whilst targeting a smaller patient group than the extended indications. With each approved indication drug prices declined in Germany and France, remained constant in the UK, Canada, and Australia, whilst they increased in the US. Negative HTA outcomes, clinical restrictions, and managed entry agreements were more frequently observed for indication extensions. Different mechanisms to account for each indication's differential benefit varied across the jurisdictions e.g., weighted-average prices (Germany, France, Australia), differential discounts (England, Scotland), clinical restrictions, and MEAs (England, Scotland, Australia, Canada). The authors concluded value-based indication-specific pricing can help to align the benefit and price for multi-indication cancer drugs.

Mills et al [237] examined marketing authorisations and HTA coverage recommendation sequences for multi-indication medicines across Germany, France, England, Scotland, Canada, Australia, and the US. The authors found that relative to subsequent indications, initial indications were more likely to receive conditional marketing authorisation, have an orphan designation, be based on single arm phase II pivotal trial evidence and lower magnitude of clinical benefit scale score. This study also reported the difference in approval times for registration (Figure 8) and reimbursement (Figure 9) for multi-indication products (first authorisation compared with subsequent authorisations). Subsequent indications had faster HTA coverage recommendation times in England and Canada. While the majority of first indications received HTA coverage recommendations across all settings, the proportion of subsequent indications with HTA coverage recommendations was lower and uptake varied considerably across settings.

Figure 8 Kaplan-Meier plots of registration approval time for multi-indication oncology products across regulatory agencies

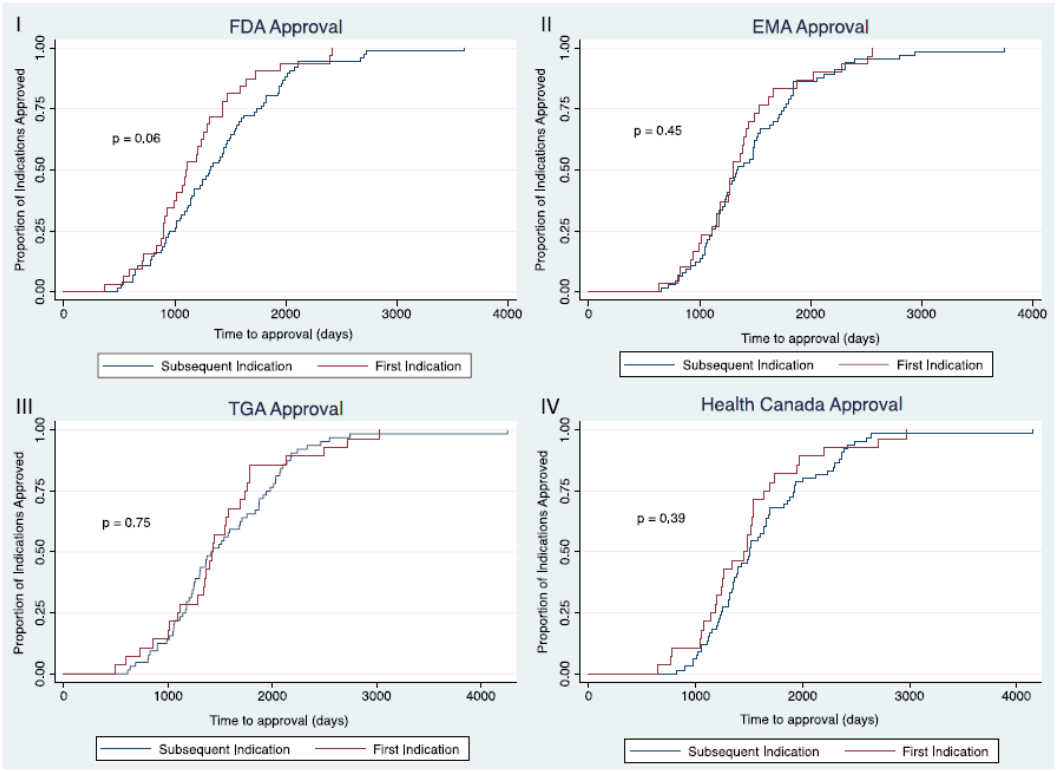
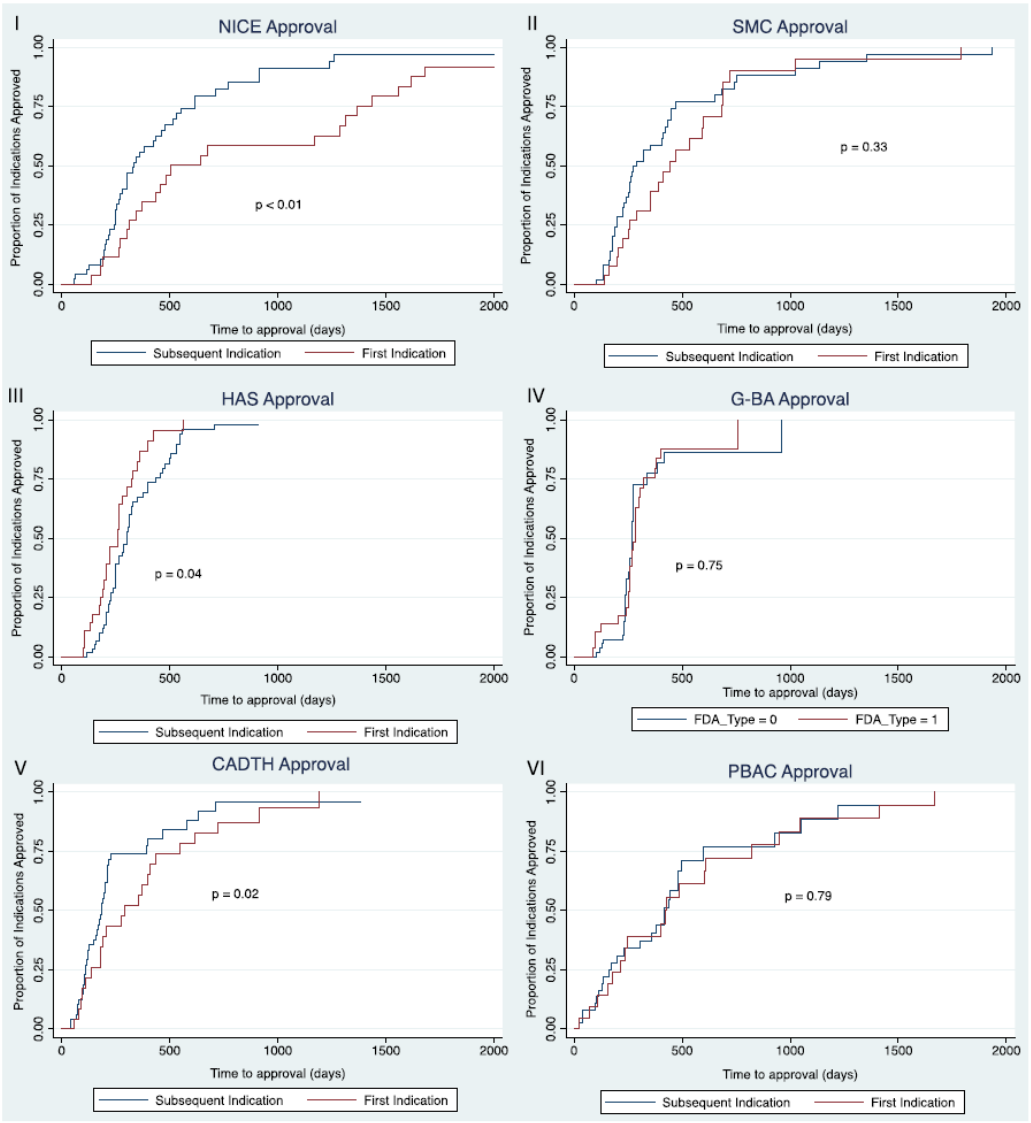


Fig. 1 Kaplan Meier plots of clinical development time for multi-indication products, defined as time from pivotal trial initiation to regulatory approval. I – Clinical development time of first vs subsequent indications in the USA. II – Clinical development time of first vs subsequent indications in Europe. III – Clinical development time of first vs subsequent indications in Canada. IV – Clinical development time of first vs subsequent indications in Australia. Abbreviations: EMA – European Medicines Agency, FDA – Food and Drug Administration (USA), TGA – Therapeutic Goods Administration (Australia)

Source: Mills et al (2023) [237]

Figure 9 Kaplan-Meier plots of HTA approval time for multi-indication oncology products



p-value calculated based on Log rank tests

Fig. 2 Kaplan Meier plots of HTA approval time for multi-indication products, defined as time from regulatory approval to HTA approval. I – HTA approval time of first vs subsequent indications in England. II – HTA approval time of first vs subsequent indications in Scotland. III – HTA approval time of first vs subsequent indications in France. IV – HTA approval time of first vs subsequent indications in Germany. V – HTA approval time of first vs subsequent indications in Canada. VI—HTA approval time of first vs subsequent indications in Australia. Abbreviations: CADTH—Canadian Agency for Drugs and Technologies in Health, G-BA – Federal Joint Committee, HAS – Haute Autorité de Santé (HAS), NICE – National Institute of Health and Care Excellence, PBAC – Pharmaceutical Benefits Advisory Committee, SMC – Scottish Medicines Consortium

p-value calculated based on Log rank tests

Source: Mills et al (2023) [237]

Conclusion

In Australia, HTA processes are conducted for a single-indication at a time, which is a consistent process internationally. Manufacturers/sponsor launch products for single-indications where the initial indication is for high severity diseases or the indication fulfils an unmet need. However, health technologies are being developed for multiple indications, which have varying degrees of clinical benefit across these patient populations. The value of first indication compared with subsequent indications can be a major challenge where price based on the

initial indication. Three methods for flow-on pricing for multi-indication products described in the literature are: 1) single price policy; 2) indication-based pricing; and 3) indirect indication-based pricing methods. In Australia, as HTA is conducted by a single-indication at a time; indirect indication-based pricing methods are applied using SPAs, RSAs, or other types of agreements. Indirect indication-based pricing methods is the most common approach identified across jurisdictions.

Why this matters?
Many products have therapeutic value over multiple therapeutic indications, and may have been developed with consideration to these multiple indications. However, HTA is typically conducted for a single indication at a time, meaning the price is set initially for that indication. Ultimately, the return to the manufacturer is based on both the price and the total volume of sales. A single price policy may lead to a higher cost to government, where price is based on the initial indication being launched, where there is strong evidence and a high clinical benefit. On the other hand, a single price policy may negatively impact access, since some lower-value indications may not be reimbursed, or where manufacturer incentives are reduced where the new therapy is for a low cost indication. Indirect indication-based pricing methods are most frequently used in Australia and comparable jurisdictions, which are linked in most cases to risk-sharing agreements, allows for confidentiality in pricing to be maintained.

7. Findings Part 3: Recent reforms

Recent changes to economic evaluation processes and methodology in Australia and internationally

a. Processes and the alignment with health technologies[18]

Advancements in methodology often takes time to develop; however there have been changes in relation to HTA methodology and processes recently, including changes to economic evaluation approaches and methodologies occurring globally.

Ten agencies have updated their methods and process guidelines since 2020 (Australia, MSAC in 2021; England and Wales, NICE in 2022; Scotland, SMC 2020-2022; New Zealand, PHARMAC in 2020; France, HAS in 2020; Germany, IQWiG in 2022; Norway, NIPH in 2021; Singapore, ACE in 2021 to 2023; South Korea, HIRA in 2021; Japan, C2H in 2022). Many of these changes with respect to HTA methodology and considerations have been discussed in Part 1 and Part 2 of this report. The guidance from these agencies covers health technologies including medicines and vaccines, as well as co-dependent technologies. However, these guidelines provide little or no reference to highly specialised therapies, such as cell and gene therapies.

Only the TLV in Sweden has published guidance (in 2021 and 2022) with respect to methods for identifying the value of precision medicines and ATMPs (see Section Part 2 New and emerging technologies of this report). To date, no treatments have been assessed under this new guidance. NICE are also currently planning to develop targeted processes and methods for cell and gene therapies, artificial intelligence and genomics. Technical guidance for these topics has not yet been issued.

b. Outcomes of reforms

Reform initiatives from Australia, Scotland and the UK are discussed in this section.

<u>Australia</u>

A review of HTA processes in Australia was conducted in December 2009. The key objectives of the HTA review in 2009 were to address the regulatory burden on businesses resulting from the HTA processes, to ensure processes were efficient, measured and proportionate. The HTA

[18] Based on Health technologies are those that are in scope of the HTA Policy and Methods Review, as per Terms of Reference. Includes: 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 defined in points 1 and 2 (i.e., co-dependent technologies); and 4) Foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.

review in 2009 focussed primarily on processes such as: the regulation of therapeutic goods for market entry; approval of funding under the MBS, as informed by the MSAC; listing of protheses under private health insurance coverage, as informed by the Prosthesis and Devices Committee (PDC); and the listing of hybrid and co-dependent technologies, informed under PBAC, MSAC and the PDC.

Reform initiatives relating to the regulatory processes and HTA pathways for reimbursement for the PBS and the MBS since 2009 include:

- MES, as a formal process, were introduced in 2010 [238] (noting that individual technologies were subject to MES like arrangements prior to 2010). The impetus for this change was to improve patient access by reimbursing drugs on the condition that further evidence is collected. Medicines recommended under this pathway are listed with a price that is justified using the existing evidence, pending a submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price. In these cases, the PBAC provides advice in relation to sources of uncertainty and specific evidence required to support a subsequent application. Pricing for medicines listed on the PBS can be altered once a product is listed, if the medicine was recommended under the Managed Entry Scheme (MES) [238]. However, uptake of MES in Australia has been low [61]. Managed agreements based on outcomes have been challenging in practice [62].
- TGA and PBAC Parallel Process was introduced for medicines in 2011 and later for vaccines in 2017. This arrangement enabled medicines to be evaluated concurrently by the TGA and the PBAC to expedite listing and subsidy of new innovative medicines in Australia. This process has led to faster access of new and innovative medicines. Positive feedback was noted from industry for implementation of this reform. Access to new specialist cancer medicines also increased as a result [239]. Although the TGA/PBAC Parallel process has accelerated the listing process, uncertainty is increased where data is less mature such as when medicines are processed under the expedited regulatory pathways.
- PBS Process Improvements were implemented in a two staged approach (based on Clause 10, Strategic Agreement 2017) [63]. Stage 1 PBS Process improvements commenced on the 1st of July 2019 including: 1) Changes to pre-submission meetings to provide additional guidance and support for complex submissions; 2) Introduction of a compulsory intent to apply step for Major and Minor submissions; and 3)

Introduction of four new transparent pathways following a positive PBAC recommendation.

Stage 2 PBS process Improvements commenced 1st of January 2021 including: 1) Changes to initial submission categories (including introduction of a single submission date); 2) Introduction of resubmission pathways for submissions not recommended by the PBAC; 3) Revised cost recovery arrangements to support implementation of Stage 2 process improvements; and 4) Other improvements, including expansion of the department's Health Products Portal functionality.

The Procedure Guidance were revised [21] along with new forms [71] to support these process improvements. The Cost Recovery Implementation Statement and Cost Recovery Administration Guidelines are also available on the Cost Recovery [240] web page.

One of the process improvements were to develop key metrics, for which data is collected and published for the time taken to list a medicine on the PBS [64]. Progress of the listing of medicines are tracked in the Medicine Status Website [241]. Medicines considered from the July 2019 PBAC meeting and onward are included in this database. The website allows a user to view the progress of an individual medicine, but does not give provide aggregate descriptive statistics for the time taken from submission to listing.

- In 2021, DoHAC commenced work to support reforms and improvements to the Prostheses List [65]. Stakeholder feedback during the consultation process included (but was not limited to), the future role of the Prostheses List Advisory Committee (PLAC), the Clinical Advisory Groups (CAGs) and their membership. Important messages the Department has received from stakeholders include the need for flexibility in the process; clear guidance material; transparency; elimination of repetition; and consistency of messaging.
  The governance structure and membership of the PLAC was considered to be preventing PLAC from effectively fulfilling its purpose (which was to provide recommendations and advice on clinical effectiveness and cost-effectiveness of devices, and other matters related to the PL to the Minister for Health and Aged Care and the DoHAC. A few of the changes included: Perceived and actual conflicts of interest are removed from the committee membership i.e., representatives from Medical Device, Private Hospitals and Private Health Insurance industries; and the

existing CAGs and Panel of Clinical Experts (PoCE) were to be re-structured into six Expert Clinical Advisory Groups (ECAGs), with up to ten members residing on each ECAG. The PLAC was modernised with a change of name, the Medical Devices and Human Tissue Advisory Committee (MDHTAC). These and other new arrangements came into place recently (1st of July 2023) [65].

- An inquiry into approval processes for new drugs and novel medical technologies were conducted over 2020 to 2021. As part of the inquiry, the Committee examined the range of new drugs and emerging novel medical technologies that are in development and progressing through the regulatory system in Australia and internationally; examine approval processes of new drugs and medical technologies with considerations for where efficiencies in the processes can be found without compromising safety, quality, and efficacy; measures to make Australia more attractive for clinical trials; and incentives to research and commercialise new drugs and medical technologies. The inquiry noted several challenges facing the existing system providing 31 recommendations (see report [12] for more details) [209].

Scotland, SMC

The SMC recently introduced a fast-track resubmission process from January 2020 for submissions where the only change is a new or improved simple Patient Access Scheme (PAS) or if the point of the resubmission is a change to the confirmed price list. This reform aims to expedite the assessment of medicines. This will allow a resubmission to proceed directly to the SMC committee with an overall assessment timeline of up to 14 weeks i.e., there is no consideration by the NDC. Submission's must meet specific criteria to be considered under the fast-track resubmission process [86]. This reform was initiated by the SMC in 2020 to manage the workflow of submissions and recognise the fast-paced development of health technologies.

England and Wales, NICE

In July 2019, NICE initiated a major review of reforms of their health technology evaluation methods guide, which outlined a 5-year strategic plan for the direction and priorities for NICE [242].

One of the motivations for change outlined was the rapid pace of healthcare innovation (treatments, practices, and technologies) and growing importance of real-world data. In terms of methods used to inform HTA, NICE have outlined they plan to implement a revised NICE process and methods manual for technologies with the Innovative Licensing and Access

Pathway and Innovative Medicines Fund arrangements. NICE also plan to develop targeted processes and methods for cell and gene therapies, artificial intelligence and genomics.

In 2022, NICE developed a 'Proportionate approach' to technology appraisals with the aim of increasing capacity to be able to produce more guidance, thereby reducing the time in conducting appraisals; and to enable decisions to be made faster [66]. NICE are currently conducting pilots on these process changes using 'live' appraisals with the aim of obtaining immediate feedback from stakeholders on the process being implementing. The aim is to eventually cover all new drugs under this process. Two different methods/streamlined approaches using the proportionate approach include: cost comparison appraisals and streamlined decision-making.

- Cost comparison approach (formerly known as 'fast track approvals'): piloted for two technology appraisals (somatrogon for treating growth disturbance in children and young people; and vutrisiran for treating hereditary transthyretin-related amyloidosis). Cost comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. The newly streamlined approach shortened timelines by 45% to 23 weeks representing the time to positive recommendation. Recommendations are made by a subset of the committee outside of formal meetings, which differs from practice in Australia. The HTA evaluation timeline for pharmaceutical in Australia is 17 weeks from sponsor submission to the PBAC meeting.

Streamlined decision-making: for technology appraisals that are beyond those suitable for cost comparison. Applies to evaluations that considered to be lower risk for patients, the NHS, stakeholders and NICE. Other improvements to efficiency within the HTA processes conducted by NICE are aimed at:

- Technical engagement: to only include when helpful for decision-making (criteria?). All technology evaluations included technical engagement by default. This step was removed in a small number of evaluations (not explicitly stated which evaluations removed the technical engagement step).
- Paired appraisals: used for the alignment of evaluation timelines where multiple appraisals are conducted in the same disease area. Previously this was managed informally, however, internal approaches were developed to manage topics in the same disease area. This process is being piloted for empagliflozin and dapagliflozin for

the treatment of chronic heart failure with preserved or mildly reduced ejection fraction (ID3945; ID1648). Small but valuable improvements to efficiency were observed.

- Handling of confidential information: NICE has partnered with CADTH and the ICER-US to develop a joint position statement on confidentiality of clinical evidence.
- Pre-specifying assumptions: NICE explored whether particular assumptions could be pre-specified at the start of an evaluation.
- Pathway appraisals: NICE are exploring the use of using a pre-built economic model to be used for ongoing evaluations, which is an approach that departs significantly from the current single technology appraisal. This approach requires long-term development and is currently being piloted over 2023-24 for technologies used in renal cell carcinoma and non-small cell lung cancer. During the consultations conducted as part of the HTA Review in February 2024, concerns were raised by stakeholders pertaining to the use of a disease specific common model. The feedback centred on concern regarding the development, implementation and use of these models, and the unintended consequences arising from resourcing and ownership needed to develop and maintain the model. Other concerns raised discussed that following the listing of an initial treatment for a particular indication, subsequent therapies would likely follow a cost-minimisation pathway. The NICE website states that they are currently assessing what principles and lessons from the pathways pilot will be incorporated into the Single Technology Appraisal (STA) process. More information about how this will be done will be provided in March 2024, with a report from the pilot appraisals (in renal cell carcinoma [ID6186] and non-small-cell lung cancer [ID6234]) expected to be published in Q2 2024 [243].

8. Appendix

Appendix 1: Relevant sources

Table 27 List of jurisdictions and agencies

Jurisdiction	Agency	Abbreviation; English translation	Website
England and Wales	National Institute for Health and Care Excellence	NICE	https://www.nice.org.uk/
Scotland	Scottish Medicines Consortium	SMC	https://www.scottishmedicines.org.uk/
Canada	Canada's Drug and Health Technology Agency	CADTH	https://www.cadth.ca/
Canada (Quebec)	*The Institut national d'excellence en santé et en services sociaux*	INESSS	https://www.inesss.qc.ca/en/home.html
New Zealand	Pharmaceutical Management Agency	PHARMAC	https://pharmac.govt.nz/
France	*Haute Autorité de Santé*	HAS; French National Authority for Health	https://www.has-sante.fr/
Germany	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen*	IQWiG; German Institute for Quality and Efficiency in Health Care	*https://www.iqwig.de/*
	Gemeinsamer Bundesausschuss	NICE; Federal Joint Committee	*https://www.g-ba.de/english/*
Norway	Norwegian Medicines Agency	NoMA	https://legemiddelverket.no/english
	Norweigan Institute of Public Health	NIPH	https://www.fhi.no/en/
Sweden	*Tandvårds- och läkemedelsförmånsverket*	TLV; Dental and Pharmaceutical Benefits Agency	https://www.tlv.se/in-english.html
The Netherlands	*Zorginstituut Nederland*	ZIN; National Health Care Institute	https://www.eunethta.eu/zin/
	European Network for Health Technology Assessment	EUnetHTA	https://beneluxa.org/HTA_procedures
Belgium	National Institute for Sickness and Disability Insurance	INAMI-RIZIV	https://www.inami.fgov.be/fr/Pages/default.aspx
	Belgium Health Care Knowledge Centre	KCE	https://beneluxa.org/HTA_procedures
Luxembourg	*Ministère de la Sécurité sociale*		https://mss.gouvernement.lu/en.html
Spain	*Agencia de Evaluación de Tecnologías Sanitarias*	AETS; Health Technology Assessment Agency	https://redets.sanidad.gob.es/
	Agencia de Evaluación de Tecnologías Sanitarias de Andalucía	AETSA; Andalusian Agency for Health Technology Assessment	https://www.aetsa.org/
	Agencia Española de Medicamentos y Productos Sanitarios	AEMPS; Spanish Agency of Medicines and Medical Devices	https://www.aemps.gob.es/?lang=en

Jurisdiction	Agency	Abbreviation; English translation	Website
	Agència de Qualitat i Avaluació Sanitàries de Catalunya	AQuAS; Agency of Health Quality and Assessment of Catalonia	https://aquas.gencat.cat/en/ajuda/mapaweb/
	Axencia de Avaliación de Tecnoloxías Sanitarias de Galicia	AVALIA-T; Galician Agency for Health Technology Assessment	https://avalia-t.sergas.gal/Paxinas/web.aspx
	Catalan Health Service	CatSalut	https://catsalut.gencat.cat/ca/inici/
	Instituto Aragonés de Ciencias de la Salud	IACS; Health Sciences Institute in Aragon	https://www.iacs.es/
	Basque Office for Health Technology Assessment	OSTEBA	https://www.euskadi.eus/web01-a2ikeost/en/
Japan	Central Social Insurance Medical Council (Chuikyo), established under the National Institute of Public Health (NIPH) and Ministry of Health Law and Welfare (MHLW)	C2H	https://c2h.niph.go.jp/en/
South Korea	Health Insurance Review and Assessment Service	HIRA	https://www.hira.or.kr/eng/main.do
	National Evidence-Based Healthcare Collaborating Agency	NECA	https://www.neca.re.kr/
Singapore	Agency for Care Effectiveness	ACE	https://www.ace-hta.gov.sg/about-us
Taiwan	The National Institute for Health Technology Assessment	NIHTA	https://www.cde.org.tw/eng/HTA/NIHTA
	National Health Insurance Administration	NIHA	https://eng.nhi.gov.tw/en/mp-2.html

ACE = Agency for Care Effectiveness (Singapore); C2H = Center For Outcomes Research And Economic Evaluation For Health (Japan); CADTH = Canadian Agency for Drugs and Technologies in Health; CatSalut = Catalan Health Service (Spain); G-BA = Federal Joint Committee (Germany); HAS = French National Authority for Health; HIRA = Health Insurance Review and Assessment Service; HTAA = health Technologies Assessment Agencies (Spain); KCE = Belgian Health Care Knowledge Centre; MSAC = Medical Services Advisory Committee (Australia); NICE = National Institute for Health and Care Excellence (England and Wales); NIPH = Norwegian Institute of Public Health; NoMA = Norwegian Medicines Agency; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PHARMAC = Pharmaceutical Management Agency (New Zealand); SMC = Scottish Medicines Consortium; NIHTA = Taiwan Society for Pharmacoeconomics and Outcome Research; TLV = Dental and Pharmaceutical Benefits Agency (Sweden); ZIN = Zorginstituut Nederland (National Health Care Institute, Netherlands).

Table 28 Website search: HTA organisations/societies and consumer representative groups

Agency	URL
Medicines Australia (MA)	https://www.medicinesaustralia.com.au/
Medical Technology Association of Australia (MTAA)	https://www.mtaa.org.au/
Rare Cancers Australia	https://www.rarecancers.org.au/
Office of Health Economics (OHE)	https://www.ohe.org/
The Professional Society for Health Economics and Outcomes Research (ISPOR)	https://www.ispor.org/
Association for Regulatory and Clinical Scientists (ARCS)	https://www.arcs.com.au/
Generic and Biosimilar Medicines Association (GBMA)	https://www.gbma.com.au/

Agency	URL
Institute for Clinical and Economic Review (ICER)	https://icer.org/

Appendix 2: Consolidated interview protocol

Time of each interview: approximately 60 minutes

Note: Interview will be audio-recorded for transcription.INTRODUCTION

I. Personal introductions

II. Interviewer introduces the research topic, explaining the aim of the overall project and the interviews:

'CHERE is undertaking a review of health technology assessment methods and policies in Australia and internationally as part of the Department of Health and Aged Care's broader HTA Review, which will inform specific reforms regarding how health technologies are assessed and funded to ensure that subsidy schemes and funding programs meet the needs of Australians into the future.

III. Informed consent:

1. Participant information sheet provided.
2. Participant informed verbally that interview will be audio-recorded.
3. Participants' questions are answered, if applicable.
4. Participant has provided signature to indicate informed consent.

OVERVIEW
Interviews will cover the following thematic lines of inquiry:

5. General understanding of international HTA processes;
6. Specific factors impacting international approaches and HTA methods used to support reimbursement;
7. Strategies for managing various forms of uncertainty;
8. Impact of recent reforms; and
9. Emerging trends and innovations.

INTERVIEW QUESTIONS

1. Briefly, could you describe the processes and methods used to inform the evaluation, pricing and purchasing/reimbursement of new health technologies in [Country]?
2. What specific policies/guidelines inform HTA submissions and evaluations? In what ways do applicable guidelines/methods strengthen/hinder the process of bringing new therapies to market?
3. Are there separate processes or special considerations in place to foster better access/health outcomes among identified equity groups (e.g., children, Indigenous, socio-economically disadvantaged, rare disease)?
4. Are there local provisions for the combined consideration of multiple sub-populations? What are the strengths/limitations of such approaches? What are the flow-on effects with respect to pricing?
5. How is (clinical, economic, financial and technological) uncertainty managed with respect to evaluation, pricing and purchasing/reimbursement?
6. What benefits, risks and limitations have you identified with respect to local approaches to HTA? In what ways have these approaches strengthened/hindered access and accountability in your context?
7. What risks/challenges/opportunities are likely to emerge in the future and how are these being addressed?
8. Is there anything else about the process for drug reimbursement [in Country] that we have not addressed that you would like to raise?

INTERVIEW GUIDE [1,2]

Thematic area	Raised	Prompted
1. What are the current approaches to evaluation, pricing and purchasing/reimbursement with respect to technologies or indications that:		
10. provide a substantial improvement in efficacy or reduction in toxicity compared to alternatives (e.g., cost-utility analysis)?	☐	☐
11. do not provide a substantial improvement in efficacy or reduction in toxicity compared to alternatives (e.g., cost-minimisation analysis)?	☐	☐
12. improve ease of use, suitability and/or reduce patient burden?	☐	☐
13. are for rare diseases and small patient groups/sub-populations?	☐	☐
14. are for populations for which there is a high unmet clinical need?	☐	☐

15. address equity concerns for specific groups, including vulnerable and disadvantaged populations?	☐	☐
16. are co-dependent?	☐	☐
17. have limited evidence of long-term outcomes?	☐	☐
2. What are the current methods/approaches to HTA with respect to:		
18. the use of weighted scales (e.g., multi-criteria decision analysis, distributional cost-effectiveness analysis)?	☐	☐
19. patient-relevant outcomes (e.g., PROMs and PREMs)?	☐	☐
20. consideration of patient preferences?	☐	☐
21. indirect and non-health benefits and harms?	☐	☐
22. extrapolation?	☐	☐
23. discounting?	☐	☐
2. How is uncertainty managed with respect to:		
24. clinical evidence?	☐	☐
25. estimation of health economic value?	☐	☐
26. population, uptake and expenditure (i.e., budget impact)?	☐	☐
27. technological innovation/obsolescence?	☐	☐
3. How and to what extent have recent reforms:		

28. addressed approaches to economic evaluation, pricing and purchasing/reimbursement with respect to the changing health technology landscape?	☐	☐
29. enabled a greater level and/or broader range of benefits?	☐	☐
30. helped manage risk?	☐	☐

Notes:

[1] The Interview Guide will not be visible to interview participants. These prompts aim to ensure thematic coverage where particular topics do not arise organically in discussion of the main lines of inquiry. Not all topic prompts are applicable to all interviewees.

[2] This draft Interview Guide is informed by an overview of the Review's papers and topics provided by the Department of Health and Aged Care. Prompts will be refined pending stakeholder responses and in collaboration with the Reference Committee.

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