



Australian Government Department of Health

Review of Life Saving Drugs Program medicines: Pompe disease

Final Review Protocol

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Introduction

On the 15th October 2018, the Australian Government Department of Health (the 'Department') engaged HealthConsult to undertake: *'a review of the medicines included on the Life Saving Drugs Program (LSDP).'*

1.1 BACKGROUND OF THE REVIEW

The LSDP, administered by the Commonwealth Department of Health, was established in the mid-1990s to provide people with rare and life-threatening diseases access to expensive medicines that were not considered to be cost effective for Pharmaceutical Benefits Scheme (PBS) listing. The LSDP currently fully subsidises 16 life-saving high cost medicines to approximately 400 patients for the treatment of 10 rare diseases.

In January 2018, following a review of the LSDP, the Australian Government committed to a number of program improvements, including a review of the medicines currently funded under the LSDP and the establishment of an Expert Panel (EP) to provide advice to the Commonwealth Chief Medical Officer (CMO).

1.2 PURPOSE OF THE REVIEW

The purpose of the Review of the LSDP review (i.e. nine disease-based reviews undertaken in three tranches) is to develop a better understanding of the real-world use of a medicine by comparing the current use performance of the medicine against the recommendations and expectations at the time of listing. The Review will assess the clinical benefits achieved through the use of LSDP medicines, ensure the ongoing viability of the program; and ensure testing and access requirements for the medicine remain appropriate.

This Review Protocol for Pompe disease medicines was prepared by HealthConsult. Its development was informed by consultations (e.g. with the EP, Pompe disease clinicians) as well as a stakeholder forum (including representatives from the Australian Pompe Association; pharmaceutical sponsor company, EP and clinicians), and a documentation review (e.g. prior reviews of LSDPs, registry publications etc). This final Review Protocol describes the methodology that will be used by HealthConsult to address each Term of Reference (ToR) for the Review of Pompe disease medicine.

1.3 TERMS OF REFERENCE

The draft ToR for the review of LSDP medicine for Pompe disease were open to public consultation from 25th February 2019 to 1st March 2019. The LSDP EP considered the draft ToR, together with comments from stakeholders, at its 8th March 2019 meeting. The ToRs were subsequently endorsed by the CMO. The seven endorsed ToRs for the Review of LSDP medicines for Pompe disease are:

- **ToR 1:** Review the prevalence of Pompe disease within Australia, both split by type (infantile onset, juvenile late-onset, adult late-onset) and overall.
- **ToR 2:** Review evidence for the management of each type of Pompe disease and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of these medicines on the program (including the validity of the tests).
- **ToR 3:** Review clinical effectiveness and safety of alglucosidase alfa in each of the treated populations. This will include analysis of LSDP patient data and international literature to provide evidence of life extension.

- **ToR 4:** Review relevant patient-based outcomes that are most important or clinically relevant to patients with each type of Pompe disease.
- **ToR 5:** Assess the value for money of alglucosidase alfa in each of the treated populations under the current funding arrangements by evaluating the benefit of the drug's treatment outcomes and cost.
- **ToR 6:** Review the utilisation of alglucosidase alfa in each of the treated populations, including storage, dispensing and evidence of patient compliance to treatment.
- **ToR 7:** Investigate developing technologies that may impact future funded access.

It is important to note that the order of the endorsed ToRs, nor the order of research questions or data sources included in the Review Protocol reflect their level of importance or the order in which the Review will occur.

ToR 1: Prevalence

This Chapter outlines the methodology to address ToR 1 “Review the prevalence of Pompe disease within Australia, both split by type (infantile onset, juvenile late-onset, adult late-onset) and overall”.

The purpose of ToR 1 is to understand the prevalence of Pompe disease within Australia and estimate the future impact of the eligible cohort on the LSDP.

2.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 1

To address ToR 1, an analysis of the prevalence of Pompe disease and by onset-type (i.e. infantile onset, juvenile late-onset, adult late-onset) in Australia will need to be undertaken. It is important to note that although the LSDP definitions include infantile onset, juvenile late-onset, adult late-onset the published literature refers only to early and late onset. *Prevalence* refers to the “number or proportion of cases, instances, etc. present in a population at a given time”.¹ Prevalence by onset-type (i.e. infantile-onset, juvenile late-onset and adult late-onset) will also be analysed. Onset types will be defined including juvenile as a form of late onset to capture full spectrum of disease. Table 2.1 presents the research questions to address ToR 1 and the data sources which will be used to answer each of the research questions. Details on the individual data sources are provided in Appendix A.

Table 2.1: Research questions to address ToR 1

ToR 1 research questions	Data sources				
	Systematic literature review	LSDP patient-level data	Diagnostic laboratory data	Pompe disease registry data	Stakeholder consultation
1. What is the prevalence of infantile onset, juvenile late-onset, adult late-onset and overall Pompe disease in Australia?	+	+	+	+	+
2. What proportion of patients with Pompe disease (and by onset type) are eligible to access treatment under the LSDP?	–	+	+	+	+
3. What proportion of eligible Pompe disease (and by onset type) patients are accessing the LSDP?	–	+	–	+	+
4. Has the prevalence of Pompe disease (and by onset type) in Australia changed since government subsidies on drugs for treating Pompe disease became available?	+	+	+	+	+
If outcomes of ToR2 indicate a change in eligibility criteria					
5. What proportion of Pompe disease patients would be eligible for the LSDP if eligibility criteria is modified?	–	–	+	+	+

Abbreviations: LSDP, life saving drugs program; ToR, term of reference

a Includes pharmaceutical sponsor

The following sections explain how each of the identified data sources will be used to inform the analysis undertaken for each of the research questions.

2.2 SYSTEMATIC LITERATURE REVIEW

A systematic literature review will be undertaken that focuses on identifying published data in peer-reviewed articles on the prevalence of Pompe disease. Published relevant literature will be searched to provide a current estimate of prevalence numbers. The search will include articles published since 2009. Table 2.2 summarises the literature search criteria that will be used to address ToR 1. Further detail on the systematic review methodology is provided in Appendix B.

Table 2.2: Literature search criteria for ToR 1

Limit	Eligibility criteria
Search terms	Synonyms for Pompe disease and an appropriate filter to identify reports relating to the incidence and prevalence of Pompe disease will guide the search. Details of the terms to be used are provided in Appendix D.
Databases	<ul style="list-style-type: none"> • EMBASE • Medline • Cochrane Library
Other means to identify relevant information	<ul style="list-style-type: none"> • Websites of regulatory agencies: TGA, PBS, FDA, MHRA, EMA • Public health statistics: ABS, AIHW, Orphanet, HealthData.gov (US), ONS (UK), StatCan (Canada), • Newborn screening studies • Manual scan of reference lists
Publication types	<ul style="list-style-type: none"> • Full text systematic reviews, literature reviews, clinical trials publications, reports and guidelines reporting on outcome measures for Pompe-specific ERT, and data cubes
Search period	<ul style="list-style-type: none"> • Articles published from 2009^a • Conference abstracts published since 2017^b
PICO	<ul style="list-style-type: none"> • Population: people diagnosed with Pompe disease • Intervention: not applicable, this is a review of prevalence • Comparator: not applicable, this is a review of prevalence • Outcomes: not applicable, this is a review of prevalence
Exclusions	<ul style="list-style-type: none"> • Wrong population: Does not include Pompe disease. • Wrong outcome: Does not investigate prevalence of Pompe disease.

Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare; EMA, European Medicines Agency; EMBASE, Excerpta Medica database; ERT, Enzyme replacement therapy; MHRA, Medicines & Healthcare products Regulatory Agency; ONS, Office for National Statistics; PBS, Pharmaceutical Benefits Scheme; TGA, Therapeutic Goods Administration; ToR, Terms of reference.

^a Prevalence was not previously reviewed in 2015 therefore a 10-year retrospective date limit will be applied

^b Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

2.3 LSDP PATIENT-LEVEL DATA

The LSDP patient-level data includes information on patients currently receiving the subsidised medicine for the treatment of Pompe disease. However, not all eligible patients may be receiving treatment with alglucosidase alfa available through the LSDP (refer to Section 2.8 on Limitations). The patient-level program data is updated through an annual re-application process. The number of patients approved for the LSDP medicine will be used to inform the prevalence of Australians diagnosed with infantile-onset, juvenile late-onset and adult late-onset Pompe disease from when the program commenced data collection on patient applications/re-applications.

It is noted that Australian Pompe disease patients who fail to meet the eligibility criteria set out by LSDP Guidelines are not registered nor monitored in the LSDP patient-level data. Hence this data source is likely to provide an underestimate of the actual prevalence. However, the LSDP patient-level data will only be one data source, albeit an important data source, used as a basis to inform the estimation of prevalence of Pompe disease in Australia. The LSDP patient-level data should provide a solid basis for informing the prevalence of Pompe disease patients who are receiving subsidised therapy within Australia.

2.4 DIAGNOSTIC LABORATORY DATA

Although the diagnosis of Pompe disease can be delivered by clinicians working across several Australian health care services, there are a limited number of laboratories in Australia that perform the testing to diagnose Pompe disease. As such, attempts will be made to access data from these laboratories to estimate the incidence of new cases of Pompe disease. Annual incidence of new cases, since 2009 (if the data is available) can then be used in conjunction with the expected mortality rate of Pompe disease to: (1) calculate and project the prevalence of Pompe disease and (2) prevalence figures and expected mortality rate can be used to calculate and project disease prevalence.

2.5 POMPE DISEASE REGISTRY DATA

HealthConsult will seek to access Pompe disease registry data. There are two key sponsor-supported registry database of relevance including:

- **Pompe Disease Registry:** This is an ongoing observational, international multi-centre, registry that tracks the routine clinical outcomes for patients with Pompe disease irrespective of treatment status ($n \approx 2,000$). It commenced in August 2004 with an estimated completion date September 2022. It is currently operated by Sanofi Genzyme with no study sites in Australia.²
- **IPA/Erasmus MC Pompe Survey:** This survey is an ongoing international questionnaire study with continuous inclusion through patient organisations. The goal of the survey is to gather information on the natural course of Pompe disease and evaluate treatment effects. The survey commenced in 2002 and consists of 14 Pompe relevant topics based on literature and expert/patient opinions in addition to the Rotterdam handicap scale, Fatigue severity scale and SF-36 scores. The survey also collects patient reported outcomes.³ As of March 2013, approximately 20 Australian patients have been reported to be part of the survey.⁴

The number of Australian patients in the registries will be factored into determining the present Pompe disease prevalence. Changes in the annual number of registered Australian patients since 2009 will also be analysed.

2.6 STAKEHOLDER CONSULTATION

Expert opinion will be used to supplement information retrieved through other ToR 1 data sources. Expert opinion, will be sought from clinicians and the peak consumer organisation, Australian Pompe Association, to inform factors affecting disease prevalence in Australia; to determine the number of Pompe disease patients being treated within and outside the LSDP; the reasons why individuals are not accessing LSDP drugs; if any Pompe disease patients are eligible for the program but elect alternative treatment; and number of patients enrolled in clinical trials.

Expert opinion will be used to supplement other ToR 1 data sources as a means of reducing uncertainty, particularly with incomplete or outdated sources of information.⁵ Guidance provided in Appendix 1 of the PBAC Guidelines (v5.0) will inform the approach that will be used to elicit and present expert opinion.

2.7 SYNTHESIS OF FINDINGS

Attempts will be made to identify specific measures of prevalence relating to:

- total prevalence versus prevalence of patients eligible for treatment with enzyme replacement therapy (ERT) under the LSDP
- proportion of eligible patients who are treated under the LSDP

- prevalence of asymptomatic individuals with a confirmed diagnosis, for instance, individuals who are positive for biomarkers of Pompe disease and display mild symptoms
- prevalence of infantile-onset (aged 0-2), juvenile-late onset (aged 2-18) and adult-late onset patients (aged 18 and over)
- prevalence of pseudo-deficient allele patients, and
- prevalence of male compared to female patients.

These indicators of disease prevalence will be comparatively analysed across different data sources to inform ToR 1 including: systematic literature review, the LSDP patient-level data, LSDP dispensing data, diagnostic laboratory datasets and Pompe disease registries.

The systematic review will provide an evidence base of secondary sources indicating the prevalence of Pompe disease patients in Australia. This evidence base will be used to address research question 1 of ToR 1.

HealthConsult may either directly extract or adapt any in-scope prevalence and/or population statistics from article inclusions. Any statistical insight into incidence rates and/or mortality rates are likely to influence total count of Pompe disease cases over time and may therefore need to be factored into calculations to determine total disease prevalence. The prevalence rates of patients with pseudo-deficient alleles (i.e. changes in the acid alpha-glucosidase *GAA* gene sequence resulting in lower *GAA* enzyme but not enough for a diagnosis of Pompe Disease⁶) are also likely to influence the total count of Pompe disease cases.

Research question 3 will be addressed by taking the number of patients observed in the LSDP patient-level dataset as a proportion of the eligible population, as determined in research question 2. The eligible population will be determined via:

- analysis of Australian diagnostic laboratory datasets that include information on patient characteristics related to the LSDP eligibility criteria, and/or
- estimation by subtracting the number of ineligible patients (such as those enrolled in clinical trials) from total disease prevalence estimated in research question 1.

Variations in the annual statistics of Pompe disease cases, pre and post introduction of the LSDP subsidised medicine, will be used to inform research question 4. Additionally, discussion pieces from authors of systematic reviews may also be incorporated into the analysis to provide context around related data, for instance, discussion on driving factors behind change in prevalence over time. The data obtained may also assist to better understand the number of new patients expected to be diagnosed annually.

The discussion will also include the applicability of the results of the trials to the population for whom ERT is available on the LSDP and, also, the population for who ERT should be available, if findings from ToR 2 indicate that a change to current eligibility criteria might be warranted.

2.8 LIMITATIONS

It is noted that some Australian Pompe disease patients may not be identified in the LSDP patient-level data. Some patients may be exclusively registered on international registries if, for instance, they have sought novel treatment modalities. While publications based on clinical trials data typically identify countries of patient recruitment sites and/or country of patient cohorts, the data in these articles are often presented at aggregate level where Australian data is mixed in with international cohorts. Attempts will be made to retrieve Australian data from commercial registries which are used for clinical trials. Without this trial data, total Australian disease prevalence calculations will likely represent an underestimate. Attempts will also be made to access data from Australian diagnostic pathology laboratories to obtain evidence to supplement the LSDP patient-level data.

The accuracy of disease prevalence calculations will rely heavily on information about Australian patient numbers in clinical trials, and commercial patient registries.

A limitation faced in ToR 1 will be the availability and completeness of identified datasets. Patient privacy guidelines will prevent the obtainment of patient-level data which can be cross-referenced to identify individuals included in multiple datasets to be used in ToR 1. This will impact estimation of the eligible population. Determination of incidence of new patients diagnosed in Australia will likely depend on access to pathology laboratory datasets. The limitation with these datasets includes potential double counting and/or duplication captured by multiple diagnostic laboratories. For example, within National Reference Laboratories (NRL) and PathWest confirmed diagnosis of enzyme activity may be remeasured in some patients and screening for Pompe disease conducted in remote laboratories. Also gaps in the data may be due to late onset patients who have yet to be screened and those that qualify for LSDP medicines and do not use it.

ToR 2: Management of Pompe disease in comparison to LSDP guidelines

This Chapter outlines the methodology to address ToR 2 “Review evidence for the management of each type of Pompe disease and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of these medicines on the program (including the validity of the tests).” An overview of the diagnosis and management of Pompe disease by onset type (including a clinical algorithm) is in Appendix C.

The purpose of ToR 2 is to:

- understand how the LSDP patient eligibility criteria (including initial and ongoing testing protocols and their validity) compares against best practice management of Pompe disease, both domestically and internationally, and
- determine which approach is the most appropriate based on available evidence if there is a variation between clinical practice and LSDP patient eligibility.

3.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 2

To address ToR 2, a comparative analysis of the evidence on the diagnosis and management of infantile-onset, juvenile late-onset and adult late-onset Pompe disease both internationally and locally, will need to be undertaken. This will then need to be compared to how this evidence aligns with the current LSDP guidelines. Furthermore, the testing methodologies adopted/endorsed by guidelines will be analysed. This includes pseudo-deficiency alleles resulting in false positive diagnoses of Pompe disease patients and establishing an initial severity criterion for infantile and juvenile onset patients. Currently, initial treatment requirements are provided for adult late-onset cohort only. Table 3.1 presents the research questions to address ToR 2 and the data sources which will be used to answer each of the research questions. Fundamentally, the research questions seek to understand how the patient eligibility criteria (including testing protocols and the validity of those testing protocols) required for access to ERT under the LSDP compare with international clinical guidelines. This includes establishing clearer transition and stopping criteria were patients are no longer responding to treatment. Details on the individual data sources are provided in Appendix A.

Table 3.1: Research questions to address ToR 2

ToR 2 research questions	Data sources		
	Systematic literature review	LSDP patient-level data	Stakeholder consultation
1. What is the current best practice model for the diagnosis and management of Pompe disease (i.e. infantile-onset, juvenile late-onset and adult late-onset)? What is the quality of evidence underpinning this approach?	+	-	+
2. What are the eligibility criteria for initial and ongoing access to LSDP medicines? ^{a, b, c} What is the quality of evidence underpinning these requirements?	+	+	+
3. Are there any inconsistencies between clinical best practice and the LSDP eligibility criteria? ^d If yes, which is more appropriate based on evidence?	+	+	+

Abbreviations: LSDP, life saving drugs program; ToR, term of reference

^a Includes initial and ongoing diagnostic methods (i.e., enzyme studies cannot differentiate between true pathogenic variants and pseudo deficiency alleles, these must be distinguished by molecular studies) ^b Includes investigating severity criteria (i.e., severity criteria only available in adult late-onset cohort, currently no criteria in LSDP guidelines for infantile-onset or juvenile late-onset) ^c Includes clearer stopping criteria and transition phases ^d Includes investigating maximum subsidised dose through LSDP, 20mg/kg per fortnight

The following sections explain how each of the identified data sources will be used to inform the analysis undertaken for each of the research questions.

3.2 SYSTEMATIC LITERATURE REVIEW

The systematic literature review will focus on identifying the clinical indications for, and management of Pompe disease with LSDP medicines. Table 3.2 summarises the literature search criteria that will be used to address ToR 2. Ideally, literature will be available to provide insight into international treatment algorithms and/or similar international programs, national/international guidance documents, testing regimes and treatment modalities for the different Pompe sub-populations (i.e. infantile-onset, juvenile late-onset and adult late-onset).

Further detail on the systematic review methodology is provided in Appendix B. The relevant PubMed search string can be found in Appendix D (refer to Section D.2).

Table 3.2: Literature search criteria for ToR 2

Limit	Eligibility criteria
Search terms	<ul style="list-style-type: none"> Synonyms for Pompe disease and an appropriate filter to identify clinical guidelines will guide the search. Details of the terms are provided in Appendix D.
Databases	<p><u>Peer reviewed articles</u></p> <ul style="list-style-type: none"> EMBASE Medline Cochrane Library <p><u>Clinical guidelines</u></p> <ul style="list-style-type: none"> Guideline Central (www.guidelinecentral.com) Australian Clinical Practice Guidelines Portal (www.clinicalguidelines.gov.au) G-I-N (www.g-i-n.net) NORD (www.rarediseases.org) AHRQ (www.ahrq.gov) SIGN (www.sign.ac.uk) NICE (www.nice.org.uk)
Other means to identify relevant information	<ul style="list-style-type: none"> PBAC PSDs for Pompe disease medicines Product information documents for Pompe disease medicines on the ARTG Other relevant websites (e.g. Rare Voices Australia)
Publication types	<ul style="list-style-type: none"> Australian and international evidence-based clinical practice guidelines on the pharmacological management of Pompe disease
Search period	<ul style="list-style-type: none"> Articles published from 2012^a Conference abstracts published since 2017^b
Exclusions	<ul style="list-style-type: none"> Guideline does investigate Pompe disease

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ARTG, Australian Register of Therapeutic Goods; EMBASE, Excerpta Medica database; G-I-N, Guideline International Network; NICE, National Institute for Health and Care Excellence; NORD, National Organization for Rare Disorders; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; SIGN, Scottish Intercollegiate Guidelines Network; ToR, Term of Reference

^a Administration and guidelines were reviewed as part of LSDP ToR 2015 review.

^b Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

3.3 LSDP PATIENT-LEVEL DATA

The LSDP patient-level data will provide real-world evidence on which medical tests are performed to determine (a) whether patients are eligible for initiation of treatment and (b) whether patients initiated on treatment are eligible for continued access to subsidised Pompe disease treatment in Australia. An analysis of the type and frequency of tests administered for LSDP application/re-application will be undertaken. This data will be required to describe what tests are currently being undertaken on patients on the LSDP and the adherence to the annual testing requirements.

3.4 STAKEHOLDER CONSULTATION

The use of expert opinion to address the research questions in the review will follow the methods described in Appendix A of the PBAC guidelines.⁷ This includes detailing the criteria for selecting experts, number of stakeholders/experts approached, number who provided information, methods used to collect responses, questions asked and others.

Questions asked of stakeholders will be aimed at obtaining information which could not be obtained through any other source. Stakeholders, including clinicians and Australian Pompe Association, will be approached to provide comments and insight into:

- the current access criteria by onset-type
- the role of the required tests in making clinical decisions and in-patient monitoring
- the ongoing access criteria for patients (i.e., infantile-onset, juvenile late-onset and adult late-onset)
- the impact of LSDP requirements on a clinician's service.

Any conflicting opinions arising through the consultation process will be managed as per guidance provided in the PBAC guidelines.⁷ As multiple sources of opinion may be available, results will be compared and their concordance (or lack thereof) will be assessed. Consequently, once assessed, a justification for the choice of data to be used in the review will be provided. As part of the assessment (where possible) stakeholders' opinions will be compared to the literature.

3.5 SYNTHESIS OF FINDINGS

The ToR 2 systematic review will seek to identify key recommendations in clinical guidelines (local and international) for diagnosing a patient with Pompe and assessing their suitability for ERT. The review will outline the current LSDP eligibility criteria that patients need to meet to obtain access to the ERT. Eligibility criteria in terms of baseline, initial response criteria, continuation criteria and the clinical utility of these tests over time will be examined. This will include subpopulation analysis where possible (e.g. infantile-onset, juvenile late-onset and adult late-onset). A discussion on whether the introduction of molecular studies as determined by guidelines for initial and ongoing eligibility criteria will also be presented. This is due to the presence of pseudo-deficient alleles resulting in false positive detection of patients. The establishment of an initial severity criterion for infantile and juvenile onset patients will also be investigated. Currently, initial treatment requirements are provided for adult late-onset cohort only. In addition the Review will also investigate clearer transition and stopping criteria where patients are no longer responding to treatment.

The quality of evidence supporting the clinical recommendations and eligibility criteria will also be assessed. Consequently, these parameters will be compared, and the more appropriate of the two will be determined based on the quality of the available evidence. Using the qualitative data gathered through stakeholder consultations, together with the secondary data sources, will provide the evidence base to answer all the research questions.

3.6 LIMITATIONS

There is the possibility that there are (a) no formal clinical guidelines for the treatment of Pompe disease, and (b) differences in clinical practice by treating physicians. In addition, clinical algorithms and patient management pathways from international sources may differ to the Australian Pompe disease pathways due to different patient demographics or national health policies. For example, treatments used in other countries may not be available in Australia. These differences will be assessed and discussed. It is also possible that not all patient tests recommended by the LSDP guidelines are performed on each patient and/or this data is not submitted to the Department as part of the application processes. Consequently, this could impact on the assessment as to whether the current recommendations and eligibility for accessing LSDP medications are being met.

ToR 3: Clinical and comparative effectiveness and safety of medicines

This Chapter outlines the methodology to address ToR 3 “Review clinical effectiveness and safety of alglucosidase alfa in each of the treated populations. This will include analysis of LSDP patient data and international literature to provide evidence of life extension.”

The purpose of ToR 3 is to review the available evidence investigating the effectiveness and safety of current LSDP Pompe disease medicine (i.e. alglucosidase alfa) and to compare this to the natural history of the disease in the absence of such treatments and the initial expectations at the time of listing on the LSDP for each onset-type (i.e. infantile-onset, juvenile late-onset and adult late-onset).

4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3

To address ToR 3, the current LSDP subsidised medicine, alglucosidase alfa, will be compared to standard treatment of care in the absence of the LSDP subsidised medicine. Comparisons based on alternate dosing schedules will also be investigated as will any evidence on the stabilisation of disease progression and/or extension of survival due to Pompe disease medicine. Table 4.1 presents the research questions to address ToR 3 and the data sources which will be used to answer each of the research questions. Details on the individual data sources are provided in Appendix A.

Table 4.1: Research questions to address ToR 3

ToR 3 research questions	Data sources		
	Systematic literature review	LSDP patient-level data	LSDP dispensing data
Clinical effectiveness and safety			
1. How does the effectiveness and safety of alglucosidase alfa compare to when it was listed on the LSDP? ^{a, b, d, e}	+	+	+
Life extension			
2. Is there evidence that alglucosidase alfa have stabilised disease progression and/or extended survival? ^{a, b}	+	+	+
3. Are the age-adjusted rates of mortality different between alglucosidase alfa treated patients and natural disease history for each Pompe onset-type? ^{a, b}	+	+	+
If outcomes of ToR2 indicate a change in eligibility criteria			
4. What is the effectiveness and safety of alglucosidase alfa in alternate eligible populations? ^{c, d, e}	+	+	+

Abbreviations: LSDP, life saving drugs program; ToR, term of reference

a Search will be restricted to capture original pivotal trials that informed the medicines inclusion on the LSDP are required to inform clinical effectiveness and safety research questions

b Search will be restricted from 2012 to identify any new evidence since the last LSDP 2015 published report with a 2-year retrospective evidence retrieval and evaluation

c Unrestricted search date as evidence has not previously been seen by LSDP EP

d Stratified by dose consistent with eligibility guidelines, as well as established/experimental dosing regimens

e Including investigating immune mediated adverse reactions, administration of concurrent immunosuppressive agents to reduce/prevent antibodies to alglucosidase alfa

The primary population of interest, patients with Pompe disease, is defined by the current LSDP eligibility guidelines, which require confirmation of the diagnosis of Pompe disease by the demonstration of deficiency of acid alpha-glucosidase (GAA) enzyme activity by prenatal diagnosis using chorionic villus biopsies and/or cultured amniotic cells or two of the following confirmatory diagnostic tests from NATA accredited laboratories:

- deficiency of acid alpha-glucosidase in dried blood spot or lymphocytes or mixed leukocytes or skin fibroblasts or skeletal muscle, or
- urinary tetrasaccharide testing indicating a diagnostic elevation of glucose tetrasaccharides and/or molecular genetic testing indicating a disease causing mutation in the acid alpha-glucosidase gene (GAA gene),
- molecular genetic testing indicating a disease causing mutation in the acid alpha-glucosidase gene (GAA gene).

Adult late-onset Pompe disease patients must present with at least one of the following treatment criteria:

- (1) *Respiratory function test.* Patients with Forced Vital Capacity (FVC), either supine or erect, less than 80% of predicted value.
- (2) *Sleep disordered breathing.* Patients with an apnoea / hypopnoea incidence of > five events/hour of total sleep time or more than two severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.
- (3) *Significant muscular weakness.* Patients with significant muscular weakness evidenced by Manual Muscle Testing (MMT) (employing the MRC score) of four or less in either limb girdle accompanied by a 6 Minute Walk Test (6MWT).

Infantile-onset Pompe disease in patients aged up to 24 months and Juvenile Late-onset Pompe disease in patients aged over 24 months and under 18 years need only a documented diagnosis with no treatment criteria qualification.⁸

Table 4.2 presents the PICO. Outcomes for all the primary endpoints and the key secondary and exploratory endpoints assessed in the studies will be presented. At a minimum, key efficacy and safety outcomes presented in the original submissions seeking reimbursement will again be presented. However additional outcomes may be presented if the findings from ToR 4 indicate that other outcomes are important from a clinical or patient perspective. Also, if outcomes of ToR 2 indicate that a change in eligibility criteria may be warranted, outcomes in alternate populations will also be presented.

Table 4.2: PICO supporting ToR 3

Criteria	Description
Study design	The primary objective of the literature search is to locate all randomised trials comparing alglucosidase alfa to placebo ^a
Population	Australian Pompe disease patients who are eligible to receive LSDP funded medicines
Intervention	Enzyme replacement therapy (ERT) <ul style="list-style-type: none"> • Alglucosidase alfa (Myozyme)
Comparator	<ul style="list-style-type: none"> • Supportive care (or placebo in initial RCT)
Outcomes	<ul style="list-style-type: none"> • Results for primary endpoints assessed by the retrieved studies will be presented • Results for key secondary and exploratory endpoints assessed by the studies will be presented • At a minimum (and to the extent that they are available), results for the following outcomes (which were judged as being important at the time the ERTs for Pompe disease were reimbursed under the LSDP) will be reported: <ul style="list-style-type: none"> ➢ incidence of and time to occurrence of key clinical events including: <ul style="list-style-type: none"> ▪ disease risk (e.g., haemoglobin, platelet, white cell, urea, creatinine, LFT measures [all prior listed items measured in infantile-onset Pompe disease], acid alpha glucosidase activity, tetrasaccharide (urine used to measure, usually)) ▪ Cardiac function (for infantile onset Pompe disease) ▪ Sleep apnoea, dysphagia, scoliosis, contractures and lower back pain ➢ lung function measures (FVC [for infantile and adult onset], FEV₁, [juvenile onset only], respiratory failure); ➢ patient height and weight ➢ degree of ventilatory use ➢ 6MWT ➢ quality of life ➢ overall survival

Criteria	Description
	<ul style="list-style-type: none"> ➤ safety and adverse events related to alglucosidase alfa treatment (including anaphylaxis, hypersensitivity and immune-mediated reactions, and risk of cardiorespiratory failure and administration of concurrent immunosuppressive agents to reduce/prevent antibodies to alglucosidase alfa) • In addition, outcomes for other endpoints that may be of interest given the findings from ToR2 will be presented (to the extent that they are available)
Other SLR considerations	<ul style="list-style-type: none"> • No study size limits will apply • Subgroup analysis: by dose (e.g. doses consistent with TGA listing, as well as experimental dosing regimens) by age (i.e., infantile-onset, juvenile late-onset and adult late-onset).

Abbreviations: 6MWT, 6-minute walk test; ERT, enzyme replacement therapy; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; LFT, Liver function test; LSDP, Life Saving Drugs Program; RCT, randomized controlled trial; MRI, magnetic resonance imaging; TGA, Therapeutic Goods Administration

a If direct head to head trials are not identified a search will be conducted for randomised trials of either the proposed medicine or the main comparator to generate an indirect treatment comparison. If no trials are suitable for an indirect treatment comparison the search will be broadened to identify nonrandomised trials.

Table 4.3 summarises the literature search criteria that will be used to address ToR 3. Further detail on the systematic review methodology, potential search terms for PubMed and other data sources are provided in Appendix D.

Table 4.3: Literature search criteria for ToR 3

Limit	Eligibility criteria
Search terms ^a	<ul style="list-style-type: none"> • Synonyms for Pompe disease and an appropriate filter to identify articles on clinical effectiveness and safety will guide the search. Details of the terms are provided in Appendix D.
Databases of peer-review literature	<ul style="list-style-type: none"> • EMBASE (Embase.com)^c • Medline (via PubMed)^d • Cochrane Library Databases (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials)^e
Other means to identify relevant information	<ul style="list-style-type: none"> • ClinicalTrials.gov^f • International Clinical Trials Registry Platform^g • Australian Clinical Trials Registry^h • Internal registries (Original PBAC funding application pivotal trials that informed the medicines inclusion on the LSDP) • Other (Hand-searching of primary articles to identify additional studies; Database of Adverse Events Notifications Data from ARTG; PBAC PSD for alglucosidase alfa; Product information documents for Pompe disease medication on the ARTG; AIHW National Death Index data and Cause of Death data; Genzyme websites, Pompe disease registry published data reports)
Publication types	<ul style="list-style-type: none"> • Studies in humans • Studies published in English and articles not published in English • Exclude: editorials, letters, non-clinical studies
Search period	<ul style="list-style-type: none"> • Evidence from the initial LSDP listing trials will be includedⁱ • Articles published from 2012 will be eligible for alglucosidase alfa^j • Conference abstracts published since 2017^k
Study exclusion criteria ^b	<ul style="list-style-type: none"> • Duplicate data • Wrong study type: Not a randomised controlled trial • Wrong population: Does not include patients with Pompe disease • Wrong intervention: Incorrect intervention (not alglucosidase alfa [Myozyme/Lumizyme]) • Wrong comparator: Not compared to the relevant comparator (placebo (or standard therapy in absence of placebo))

Abbreviations AIHW, Australian Institute of Health and Welfare; ARTG, Australian Register of Therapeutic Goods; EMBASE, Excerpta Medica database; LSDP, Life Saving Drugs Program; MeSH, medical subject headings; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; RCTs, Randomised Controlled Trials

a Potential search terms are located in Appendix D

b Selection process will be adapted when relying on an indirect comparison of randomised trials or nonrandomised evidence

c <https://www.embase.com>

d <https://www.ncbi.nlm.nih.gov/pubmed>

e <https://www.cochranelibrary.com>

f <https://clinicaltrials.gov>

g <https://www.who.int/ictrp>

h <http://www.anzctr.org.au/>

i Search will be restricted to capture original pivotal trials that informed the medicines inclusion on the LSDP are required to inform clinical effectiveness and safety research questions

j Search will be restricted from 2012 to identify any new evidence since the last LSDP 2015 published report with a 3-year retrospective evidence retrieval and evaluation

k Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

4.2 SYSTEMATIC LITERATURE REVIEW

A systematic literature review will be conducted to address ToR 3. From this literature, the effectiveness and safety of alglucosidase alfa will be assessed. The primary objective of the systematic literature review is to identify all RCTs in the proposed population to allow a comparison of the effectiveness and safety of the medicines in the trial setting with effectiveness and safety of the medicines as observed in practice in LSDP patients.

The systematic literature review will be conducted in accordance with PBAC Guidelines (v 5.0). If necessary (e.g. if data for a key patient relevant endpoint are not captured by RCTs), data from RCTs will be supplemented with data from non-randomised studies (e.g. cohort studies, case-control studies and quasi-experimental studies). Outcomes will be directly related to the quality and/or length of a patient's life and will constitute the best available clinical evidence to support the effectiveness and safety of the LSDP medicine. The study selection process for each search will be presented in a PRISMA flowchart (see Appendix B, Section 0). A list of included trials and excluded trials and reasons for exclusion will be provided. If an indirect comparison is required, a network diagram will be provided to show common reference links. Heterogeneity and potential for bias within and across trials will be assessed. Important differences in quality of methods of trials, differences in patient characteristics, differences in circumstances of use of treatment and the potential for such differences to confound results will be discussed. In addition, the appropriateness of the endpoints assessed in the trials and methods of statistical analysis of those endpoints will also be assessed.

Original PBAC funding application pivotal trials that informed the medicines inclusion on the LSDP will be identified in a separate systematic literature review search. In addition to the published evidence, the sponsor of the medicine will be invited to provide unpublished clinical study reports (CSRs) relating to any potentially relevant trials.

4.3 LSDP PATIENT-LEVEL DATA

Treating clinicians who wish to apply for their patients to receive the LSDP subsidised medicine are required to declare that their patient meets the criteria for initial and ongoing eligibility to access subsidised treatment. As part of the LSDP subsidised medicine re-application process, clinicians must demonstrate clinical improvement in their patients or stabilisation of the patient's condition to support ongoing eligibility for the treatment of Pompe disease. Hence this information is captured in the LSDP patient-level dataset.

To inform research question 1 (clinical effectiveness and safety in trials versus outcomes observed in patients on the LSDP), an analysis of the LSDP patient-level data will be undertaken to assess the impact of alglucosidase alfa on outcomes over time. The results of these analyses will be compared against the pivotal trial estimates that informed the LSDP medicine listing. The data will also be analysed to assess the impact, if any, of increasing weight/dose/age/comorbidities on respiratory, sleep, skeletal muscle, myopathy muscle weakness and cerebrovascular outcome events. Individual patient trajectories and dose response curves will also be generated. Rates of adverse events will be compared and contrasted across dose, age, date of diagnosis and again compared to original pivotal trial results. The limitations to this analysis are discussed in Section 4.6.

To inform research questions 2 and 3 (stabilised disease progression and/or life extension), an analysis of LSDP patient-level data will be used to describe the demographic profile (including age, gender) of patients. Together with data on the date of commencement and cessation, profiles of the effect of the medicine on stabilising disease progression and/or life extension and mortality in the Australian population accessing LSDP medicine for Pompe disease will be generated. This data will be compared to the natural history of the

disease, mortality and the stabilised disease progression and/or life extension effects of Pompe disease medicine identified in the systematic literature review.

4.4 LSDP DISPENSING DATA

LSDP patient-level data linked to LSDP dispensing data will allow analysis to assess the impact of variations around recommended dose regimens on the clinical effectiveness over time as well as the impact of age on outcomes. These analyses will inform research question 1 to 3. The analysis will include descriptive statistics on date of dispensing, date of infusion, number of days between dispensing and dispensed amount, supplemented by analysis of clinical notes (where appropriate). Together this information will inform whether there are any clinical trends with variations in dose and/or age. Additional analysis will be presented comparing consistencies in dosing of alglucosidase alfa from the recommended doses in the original pivotal trials and the TGA recommended dose in the product information (PI).

4.5 SYNTHESIS OF FINDINGS

Research question 1 will be informed by an analysis of the totality of the available published evidence (and any relevant unpublished evidence that may be provided by sponsors). Additional evidence that has been generated since the PBAC's consideration of the products listed on the LSDP will also be analysed. Research question 1 will also be informed by the outcomes in the LSDP patient level dataset. All analyses will be supplemented by any evidence identified in the systematic literature review relating to clinical effectiveness and safety generated at the time of PBAC's consideration of the products listed on the LSDP compared to post 2012 (i.e. post 2015 review).

Research questions 1 will require additional analysis to include a comparative analysis of the effectiveness and safety of the medicines listed on the LSDP based on the published evidence (and unpublished evidence provided by the sponsor, if any) and based on analysis of patient-level data from the LSDP program. To the extent that it is possible, differences in respiratory, sleep, skeletal muscle myopathy and cardiomyopathy endpoints will be assessed. Also, LSDP dispensing data will be used to analyse trends (by descriptive statistics on date of dispensing, infusion, days between dispenses and amount) to confirm consistency in efficacy against original trials, as well as exploring the impact of patient compliance to treatment (note that compliance will be further explored in ToR 6). Finally, we will compare current doses to the dosing used in the original trials to the recommended dose in the TGA approved product information.

Research questions 2 and 3 will be informed by the systematic literature review on the natural history of Pompe disease and stabilised disease progression and/or mortality/survival, analysis of LSDP patient-level data including LSDP medication duration. To gain a comprehensive understanding on the effects of LSDP medicines on patient longevity and age-adjusted survival, an analysis of AIHW National Death Index data and Cause of Death data linked to LSDP patient-level data will be sought.

The information gathered for ToR 3 will be presented in accordance with the guidance provided in Section 2 of the PBAC guidelines 5.0. For example, the information in the publications identified by the systematic literature review will include assessment of internal validity; a presentation of the intervention(s) and comparators assessed by the trials, patient characteristics in the trials, endpoints assessed by the trial and the methods of statistical analysis, efficacy and safety outcomes of the trials. Any relevant subgroup analyses or meta-analysis will also be presented. Finally, treatment effect variation that is related to differences between the trial setting and the Australian setting will be discussed. The discussion will also include the applicability of the results of the trials to the population for whom ERT is available on the LSDP and, also, the population for whom ERT should be available, if findings from ToR 2 indicate that a change to current eligibility criteria might be warranted.

4.6 LIMITATIONS

The quality of LSDP patient-level data could represent a major limitation in the evaluation of effectiveness. Factors that may cause bias in the LSDP patient-level data include:

- loss to follow up (patients that discontinue treatment due to disease progression, mortality or adverse events; overseas relocation; personal choice; participation in a clinical trial)
- missing/inconsistent outcome data
- deviations from recommended dose regimen
- variations in time on treatment
- age of initiation of treatment
- severity of disease.

Sensitivity analysis will be conducted to test the robustness of certain assumptions from the patient-level program data and separate results on particular outcomes if the data is available.

Other limitations include:

- A lack of a control group in patients on the LSDP program as data is collected on symptomatic patients who qualify for LSDP funded medicines only. There is no asymptomatic or 'control group' of patients that have Pompe disease and who do not qualify for LSDP funded medicines. The Pompe registry may provide information on patients not eligible for LSDP medicines. This will be further investigated and utilised if suitable.
- The difficulty in analysing the difference between progression of the natural history of Pompe disease versus the impact of aging.

Overall, if the patient level program data has a high level of uncertainty it may not be appropriate to perform inferential statistics and descriptive statistics may be more appropriate.

ToR 4: Relevant patient-based outcomes

This Chapter outlines the methodology to address ToR 4 “Review relevant patient-based outcomes that are most important or clinically relevant to patients with each type of Pompe disease.”

The purpose of ToR 4 is to identify the treatment outcomes that are highly valued by patients with Pompe disease and their clinicians.

5.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 4

To address ToR 4, an analysis of patient-based outcomes for patients receiving the LSDP subsidised medicine will need to be undertaken. ‘Patient-based outcomes’ are also known as ‘patient-centred outcomes’ or ‘patient-reported outcomes’ (PRO) and refer to “how health services and interventions have, over time, affected a patient’s quality of life, daily functioning, symptom severity, and other dimensions of health which only patients can know”.⁹ Table 5.1 presents the research questions to address ToR 4 and the data sources which will be used to answer each of the research questions. Details on the individual data sources are provided in Appendix A.

Table 5.1: Research questions to address ToR 4

ToR 4 research questions	Data sources		
	Systematic literature review	LSDP patient-level data	Stakeholder consultation
1. What outcomes are most important to patients with Pompe disease and their clinicians, by onset type, who are being treated with the subsidised LSDP medicine?	+	+	+
2. How can administration of the LSDP be improved to help patients with Pompe disease and their clinicians? Does the administration differ for the different onset cohorts?	–	–	+

Abbreviations: LSDP, life saving drugs program; ToR, term of reference

The following sections explain how each of the identified data sources will be used to inform the analysis undertaken for each of the research questions.

5.2 SYSTEMATIC LITERATURE REVIEW

The systematic review will focus on identifying Pompe disease PROs related to ERT. Table 5.2 summarises the literature search criteria that will be used to address ToR 4. Further detail on the systematic review methodology is provided in Appendix B.

Table 5.2: Literature search criteria for ToR 4

Limit	Eligibility criteria
Search terms	Synonyms for Pompe disease and an appropriate filter to identify reports relating to the incidence and prevalence of Pompe disease will guide the search. Details of the terms to be used are provided in Section D.4 of Appendix D.
Databases of peer-review literature	<ul style="list-style-type: none"> • EMBASE • Medline

Limit	Eligibility criteria
	<ul style="list-style-type: none"> • Cochrane Library
Other means to identify evidence	<ul style="list-style-type: none"> • Clinical trial articles included for analysis in ToR 3 • Clinician input and Clinician international sponsor registry data (e.g. Pompe Registry) • Scan for relevant grey literature, including reports from Pompe disease patient organisations and peak bodies • Scan of authoritative social media^a, blogs, and self-help websites for PROs and PRO-like patient concerns regarding their treatment experience • Patient-centred outcomes research online resources such as: <ul style="list-style-type: none"> ➢ PCORI (www.pcori.org) ➢ ISPOR (www.ispor.org) ➢ The Hastings Center (www.thehastingscenter.org) ➢ PROMIS (www.healthmeasures.net) ➢ COMET (www.comet-initiative.org)
Publication types	<ul style="list-style-type: none"> • Full text reviews, clinical trials, reports and guidelines reporting on patient-centred outcome measures for the treatment of Pompe disease. • English language and reputable trials not published in English (translated by an external provider)
Search period	<ul style="list-style-type: none"> • Articles published from 2012^b • Conference abstracts published since 2017^c
Study exclusion criteria	<ul style="list-style-type: none"> • Does not relate to patients with Pompe disease. • Does not relate to patient-centred outcomes. • A patient questionnaire or outcome measurement tool without reporting on results.

Abbreviations: CAG, Clinical Advisory Group; COMET, Core Outcome Measures in Effectiveness Trials; EMBASE, Excerpta Medica database; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LSDP, Life Saving Drugs Program; PCORI, Patient-Centered Outcomes Research Institute; PRO, patient reported outcome; ToR, Term of Reference.

^a Social media sites include Pompe Disease Registry and IPA/Erasmus MC Pompe Survey

^b Search will be restricted from 2012 to identify any new evidence since the last LSDP 2015 published report with a 3-year retrospective evidence retrieval and evaluation

^c Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

5.3 LSDP PATIENT-LEVEL DATA

The LSDP patient-level data contains patient monitoring and outcomes data related to the quality of life whilst on ERT. This data source will provide both the data and the domains or measures of quality of life (from PRO measures or PROM tools) that will be cross-referenced with findings from the ToR 4 systematic review and stakeholder consultations to address research question 1.

5.4 STAKEHOLDER CONSULTATION

HealthConsult intend to consult with (i) consumers and/or consumer advocacy groups (e.g. Australian Pompe Association), (ii) clinicians and (iii) the sponsor. Input from consumers is crucial in addressing all ToR 4 research questions. The collection and reporting of expert opinion from patients, clinicians and the sponsor will be conducted in accordance with guidance provided in Appendix 1 of the PBAC Guidelines v.5.0.⁵

The stakeholder consultation process will be designed to gather data to address ToR 4 research questions. The gathering of stakeholder input may include focus groups, an online survey, webinar(s) and/or one-on-one interviews (by telephone, face-to-face and/or via videoconference). Prior to the stakeholder consultations, all invited individuals will be provided with a stakeholder interview/forum protocol (except those providing input by online survey). The protocol will explain the purpose of the interviews/forums as well as include a list of open-ended questions which will be used to facilitate discussions. The online survey will begin by setting the context through a brief presentation of information prior to commencement of the survey.

Stakeholder consultations will begin with a presentation of patient reported outcomes identified in the literature review and analysis of the LSDP patient-level dataset. The forum and/or interviews will then open to a facilitated group discussion where participants are given the opportunity to describe their experience with LSDP medicines and what outcomes are most important to them.

5.5 SYNTHESIS OF FINDINGS

In addressing the research questions, attempts will be made to stratify patients (where appropriate) by: onset type, age, gender and/or severity/ disease progression.

Thematic analysis of stakeholder input gathered against each question will be undertaken to identify the most valued patient-relevant outcomes by stakeholder group. This analysis will inform research questions 1 and 2.

5.6 LIMITATIONS

Development and/or refinement of PROs and PRO measures (PROMs) is a highly specialised area of research. It typically involves rigorous needs analysis, conceptualisation, testing, and validation^{10, 11} (i.e. beyond the activities to be undertaken in ToR 4). Therefore, further study may be required to test the validity of ToR 4 PROs identified as being important to LSDP patients, for instance, assessing if PROs are indeed a direct result of taking the Pompe disease medicine funded under the LSDP.

Being a rare disease, Pompe disease patient populations are inherently small. As such, PROM tools to measure Pompe disease-specific PROs are unlikely to have been developed.

It is unlikely that requested clinician and/or sponsor registry data will be obtainable at the patient level therefore any analysis will be restricted by the format in which it is provided.

ToR 5: Value for money of LSDP Pompe disease medicines

This Chapter outlines the methodology to address ToR 5 “Assess the value for money of alglucosidase alfa in each of the treated populations under the current funding arrangements by evaluating the benefit of the drug’s treatment outcomes and cost.”

The purpose of ToR 5 is to conduct an economic analysis assessing the costs of the medicines funded under the LSDP relative to the benefits they provide.

6.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 5

To address ToR 5 an economic analysis of the Pompe disease medicine funded under current LSDP arrangements will be undertaken. If findings from ToR 1 indicate that changes to the funding criteria are warranted then an economic analysis under alternate funding arrangements will also be considered. Consistent with all Government investments an economic model will be developed to provide Government with a standard output of value for money (e.g. QALY or ICER). Also, to ensure the ongoing sustainability of the LSDP program funded by the Australian Government an economic model will be required to investigate whether the actual costs are consistent with predicted costs as included in the initial LSDP listing. The type of economic model developed to address ToR 5 will take into consideration the availability of evidence, as identified through the review process. Table 6.1 presents the research questions to address ToR 5 and the data sources which will be used to answer each of the research questions. Details on the individual data sources are provided in Appendix A.

Table 6.1: Research questions to address ToR 5

ToR 5 research questions	Data sources						
	Systematic literature review ^a	LSDP patient-level data	LSDP dispensing data	LSDP pricing data	PBAC submissions	MBS, PBS, AR-DRGs	Stakeholder consultation ^b
1. What is the total annual cost of treating a patient with Pompe disease with the LSDP medicine by onset type? Is this different to what was expected at the time the medicine was included on the LSDP (e.g. actual vs predicted)?	-	+	+	+	+	-	+
2. What difference in quality of life is estimated for treated and untreated patients by onset type of Pompe disease? Is this different to what was expected at the time the medicine was included on the LSDP (e.g. actual vs predicted)?	+	+	-	-	+	-	-
3. What difference in survival is estimated for treated and untreated patients by onset type of Pompe disease? Is this different to what was expected at the time the medicine was included on the LSDP (e.g. actual vs predicted)?	+	+	-	-	+	-	-

ToR 5 research questions	Data sources						
	Systematic literature review ^a	LSDP patient-level data	LSDP dispensing data	LSDP pricing data	PBAC submissions	MBS, PBS, AR-DRGs	Stakeholder consultation ^b
4. How do the costs and outcomes associated with treating each onset type of Pompe disease with LSDP medicines compare with the costs and outcomes of standard of care?	+	+	+	+	+	+	+

Abbreviations: AR-DRGs, Australian Refined – Diagnosis Related Groups; LSDP, Life Saving Drugs Program; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Schedule; PBAC, Pharmaceutical Benefits Advisory Committee; ToR, term of reference

IMPORTANT NOTE: onset type refers to infantile onset, juvenile late-onset and adult late-onset Pompe disease

^a Includes HTA websites

^b only required if other data sources do not yield the required information

The following sections explain how each of the identified data sources will be used to inform the analysis undertaken for each of the research questions.

6.2 SYSTEMATIC LITERATURE REVIEW

Two systematic literature reviews (described under Table 6.2) will be conducted to source information for ToR 5. These systematic literature reviews will focus on economic evaluations and quality of life. Table 6.2 summarises the literature search criteria that will be used to address ToR 5. The search strings to be used in the literature search are based on Canadian Agency for Drugs and Technologies in Health's (CADTH) Database Search Filters.¹² The relevant PubMed search string can be found in Appendix D (refer to Section D.5). Further detail on the systematic review methodology is provided in Appendix B.

Table 6.2: Literature search criteria for ToR 5

Limit	Eligibility criteria
Search terms	<ul style="list-style-type: none"> Synonyms for Pompe disease and an appropriate filter to identify economic evaluations and quality of life measures will guide the search. Details of the terms are provided in Section D.5 of Appendix D.
Databases	<ul style="list-style-type: none"> EMBASE Medline Tufts Medical Centre CEA Registry University of York Centre for Reviews and Dissemination Health Economic Evaluations Database (HEED)
Other means to identify relevant information	<ul style="list-style-type: none"> Websites of HTA and reimbursement agencies: NICE, CADTH, SMC Manual scan of reference lists of included articles
Publication types	<ul style="list-style-type: none"> Full text systematic reviews, literature reviews, clinical trial publications, economic evaluation reports, and reimbursement application reports Available in English
Search period	<ul style="list-style-type: none"> Articles published from 2012^a Conference abstracts published since 2017^b
Study exclusion criteria	<ul style="list-style-type: none"> Does not relate to patients with Pompe disease For the search of economic evaluations: Does not include an economic model For the search on quality of life: Does not include quality of life scores

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, Cost-Effectiveness Analysis; EMBASE, Excerpta Medica database; HEED, Health Economic Evaluations Database; HTA, Health Technology Assessment; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium

^a Search will be restricted from 2012 to identify any new evidence since the last LSDP 2015 published report with a 3-year retrospective evidence retrieval and evaluation

^b Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

- (1) An economic evaluation requires articulation of health states that reflect the key possible clinical presentations of Pompe disease (infantile-onset, juvenile late-onset and adult late-onset). The first search of peer-reviewed literature, including EMBASE, Medline, Tufts Medical Centre CEA Registry, the University of York Centre for Reviews and Dissemination and the Health Economic Evaluations

Database (HEED) will be conducted in order to identify published economic evaluations on Pompe disease.

To supplement these database searches, the HTA agency websites of the National Institute for Health and Care Excellence (NICE), the CADTH, and the Scottish Medicines Consortium (SMC) will be searched for relevant economic evaluations. Past submissions to the PBAC and LSDP for Pompe disease will also be reviewed. The purpose of these searches is to use existing published work to inform the development of the economic evaluation for this review, including the health states of the model, and structural variables such as cycle length and time horizon.

Any models sourced from the literature will be assessed based on their relevance to the funding of LSDP medicines. In particular the health states employed in the economic evaluation should be consistent with the major clinical complications of Pompe disease. If none of the models identified are appropriate for the review, health states and outcomes will be identified from the clinical literature and an economic evaluation will be constructed which is consistent with PBAC guidelines. The results of this literature review will address research question 1 of this ToR and will subsequently be used in the development of the economic model for research question 4.

- (2) The second search will seek to identify information on mortality and quality of life for patients with Pompe disease. A systematic literature review on the impact of LSDP treatment on mortality and quality of life is being undertaken to address ToR 3. Therefore, those results will be considered prior to any additional search being undertaken for ToR 5. This search will inform research questions 2, 3 and 4.

Quality of life outcomes will be modelled by using peer-reviewed literature to assign utility values to the health states of the model. An alternative methodology will involve mapping quality of life scores to SF-36 physical component score (PCS) and mental component score (MCS) using the LSDP patient-level data. The literature search conducted for quality of life measures will identify publications reporting utility values for the desired health states, or methodologies for mapping the SF-36 to utility values. Both methodologies will be used to address research question 2.

6.3 LSDP PATIENT-LEVEL DATA

The LSDP patient-level data will be analysed to inform what non-LSDP medicines are used in the treatment of Pompe disease. The use of medicines unrelated to Pompe disease will be distinguished from those that are related by consulting with clinicians regarding which non-LSDP medicines they use to manage the symptoms and complications of the disease. Medicines not related to the treatment of Pompe disease will be excluded from the modelled economic evaluation.

The list of concomitant medicines for each Pompe disease patient will be used to calculate the amount of drug use for the average patient on treatment with LSDP medicines. This resource will be used to address research question 1 of ToR 5 and subsequently in research question 4.

In addition to the list of concomitant medicines to be generated from patient level data from the LSDP program, available SF-36, PCS and MCS will be mapped to utility scores to address research question 2.

6.4 LSDP DISPENSING DATA

The LSDP dispensing data will be used to calculate how much of the drug was dispensed to each patient in order to calculate the cost of treating a patient for a year. This will be used to address research question 1 and to construct the economic evaluation for research question 4.

6.5 LSDP PRICING DATA

The unit costs obtained from the LSDP pricing data will be used to calculate the total cost of LSDP medicines per patient. This analysis will be conducted separately for each Pompe disease medicine on the LSDP. The cost of treating a patient using LSDP medicines will be used to inform research questions 1 and 4.

6.6 PBAC SUBMISSIONS

The approach to the economic evaluation taken in previous submissions to the PBAC or LSDP will be considered in the development of the economic evaluation. This will include the type of economic evaluation (e.g. cost-effectiveness or cost-utility), computational methods (e.g. Markov process, microsimulation, decision tree), time horizon, and any other relevant parameters. Any issues the PBAC had with the economic evaluations presented will also be considered.

6.7 MBS, PBS, AR-DRG COST WEIGHTS AND NATIONAL EFFICIENT PRICE DATA

Unit costs for resources used in the management of Pompe disease will be sourced in accordance with guidance contained in the Manual of resource items and their associated unit costs.¹³ For example, the MBS schedule will be used to source unit costs for medical services, the PBS schedule will be used to source unit costs for medicines, and AR-DRG cost weights and the national efficient price will be used to source unit costs for episodes of hospitalisation. Unit costs will be used to address research questions 1 and 4.

6.8 STAKEHOLDER CONSULTATION (IF REQUIRED)

If values for inputs to the economic evaluation cannot be sourced from higher levels of evidence according to the hierarchy of evidence (as described in Sections 6.2 to 6.7), expert opinion will be sought. The collection and reporting of expert opinion from patients and clinicians will be conducted in accordance with guidance provided in Appendix 1 of the PBAC Guidelines v.5.0.⁷ Expert opinion may include data obtained through surveys that collect clinician time and/or sponsor registry aggregate data.

6.9 SYNTHESIS OF FINDINGS

The economic evaluation will be constructed and reported in accordance with the guidance provided in the PBAC guidelines⁷, which specify the elements of the full economic model to be presented including:

- the type of economic evaluation, computational methods, and health states
- the costs associated with the treatment options, and
- the quality of life for patients with Pompe disease by onset type.

Research question 4 will be addressed by integrating information assembled in addressing the previous research questions. Costs and outcomes for LSDP eligible patients treated with alglucosidase alfa and for standard of care will be reported. Results will also be presented by onset type. Standard of care will be clearly defined. This may include ERT or non-specific standard of care therapies. Pair-wise comparisons will be developed to compare treatment options. The 2015 Review will be consulted for any information relevant to the development of the economic evaluation.

Validation will be performed as per the PBAC guidelines.⁷ Internal validation will be performed by using traces to examine the flow of patients through the model, and by checking the change in the final results due to changes in other model parameters to ensure that the logic of the model is correct. External validation will be performed by comparing the model traces and results with empirical data and by comparing the model to other

valid modelled economic evaluations of Pompe disease (if available). Inclusion of indirect costs in economic models (e.g. days off work, missed school, carer burden etc) and societal perspective economic evaluations are not accepted by PBAC. However, this review will seek to gather narrative on these issues through the stakeholder consultations so that they can be included in the discussion of value for money in the Review Report.

6.10 LIMITATIONS

The most significant limitation in ToR 5 is that the clinical evidence may not be sufficient to produce a high-quality economic evaluation or to allow for meaningful external validation. The validity of any economic evaluation depends on the quality of the evidence. In the case of Pompe disease, it is likely that relatively few clinical studies exist, and the ones that have been conducted are likely to have recruited low numbers of patients (i.e. due to it being a rare disease). An additional issue is that modelling of surrogate outcomes to patient-relevant outcomes such as mortality and quality of life may be required. Such modelling may decrease confidence in the results of the economic evaluation. These limitations may impact important elements of the economic evaluation, such as the outcome to be modelled, which cannot be decided on until the clinical evidence is reviewed. These decisions will be based on the quality of the evidence uncovered during the review and through discussion with the LSDP EP.

ToR 6: Utilisation of LSDP Pompe disease medicines

This Chapter outlines the methodology to address ToR 6 “Review the utilisation of *alglucosidase alfa* in each of the treated populations, including storage, dispensing and evidence of patient compliance to treatment.”

The purpose of ToR 6 is to review how LSDP funded medicines are used to ensure quality use of medicines. This includes analysing patient doses, duration of treatment, and patient compliance.

7.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 6

To address ToR 6, a review of the utilisation of LSDP Pompe disease medicine by onset types, including the way they are stored and dispensed, and evidence of patient compliance to treatment, will need to be undertaken. Table 7.1 presents the research questions to address ToR 6 and the data sources which will be used to answer each of the research questions. Details on the individual data sources are provided in Appendix A.

Table 7.1: Research questions to address ToR 6

ToR 6 research questions	Data sources					
	Systematic literature review ^a	LSDP patient-level data	LSDP dispensing data	LSDP pricing data	PBAC submissions	Stakeholder consultation
Utilisation						
1. How many patients (by onset type, by year and in total) have been treated under the LSDP? How does this compare with expectations at the time the medicine was included on the LSDP?	-	+	+	-	+	-
2. How many units (by onset type, by year and in total) have been dispensed under the LSDP? How does this compare with expectations at the time the medicine was included on the LSDP?	-	+	+	-	+	-
3. What is the expenditure (by onset type, by year and in total)? How does this compare with expectations at the time the medicine was included on the LSDP? ^b	-	+	+	+	+	-
4. What is the rate of change in patient numbers, units, and expenditure year on year and overall? How does this compare with expectations at the time the medicine was included on the LSDP?	-	+	+	+	+	-
5. Has there been utilisation beyond the eligibility criteria?	+	+	+	-	+	+
6. What quantity and value of LSDP medicine is wasted? Has this changed over time?	-	-	+	+	-	-
Compliance						
7. What is the average duration (and distribution around duration) of treatment?	-	+	+	-	-	+

ToR 6 research questions	Data sources					
	Systematic literature review ^a	LSDP patient-level data	LSDP dispensing data	LSDP pricing data	PBAC submissions	Stakeholder consultation
8. What is the average dose (and distribution around average dose)? How does this compare to the approved ^c use of the medicine?	+	+	+	-	+	+
9. What is the average interval between doses (and distribution around this interval)? How does this compare to the approved use of the medicine?	+	+	+	-	-	+
10. Have patients had treatment breaks? If so, what proportion of patients and why?	+	+	+	-	-	+
Drug storage						
11. Is there variation in storage and dispensing processes by drug custodians (e.g. pharmacies or administrators)?	+	-	+	-	-	+

Abbreviations: LSDP, Life Saving Drugs Program; PBAC, Pharmaceutical Benefits Advisory Committee; ToR, term of reference

IMPORTANT NOTE: onset type refers to infantile onset, juvenile late-onset and adult late-onset Pompe disease

^a Includes Product Information

^b Including the application of PBS like pricing policies

^c Regulatory (such as TGA) and LSDP approved doses

As part of addressing the research questions above, the analysis will examine trends on compliance by age, gender etc for each question. The following sections explain how each of the identified data sources will be used to inform the analysis undertaken for each of the research questions.

7.2 SYSTEMATIC LITERATURE AND DOCUMENTATION REVIEW

A systematic literature review will be conducted to inform patient compliance with Pompe disease medicine. Information sought will be on appropriate dosage schedules and usage outside of guidelines. Table 7.2 presents the search strategy. The relevant PubMed search string can be found in Appendix D (refer to Section D.6). Further detail on the systematic review methodology is provided in Appendix B.

Table 7.2: Literature search criteria for ToR 6

Limit	Eligibility criteria
Search terms	<ul style="list-style-type: none"> Synonyms for Pompe disease and an appropriate filter to identify publications on treatment compliance will guide the search. Details of the terms are provided in Section D.6 of Appendix D.
Databases	<ul style="list-style-type: none"> EMBASE Medline Cochrane library
Other means to identify relevant information	<ul style="list-style-type: none"> PBAC PSDs Manual scan of reference lists of included articles Medicine Product Information (TGA) LSDP documents (Australian Government Department of Health)
Publication types	<ul style="list-style-type: none"> Full text systematic reviews, literature reviews, clinical trial publications, and reimbursement application reports Available in English
Search period	<ul style="list-style-type: none"> Articles published from 2009^a Conference abstracts published since 2017^b
Study exclusion criteria	<ul style="list-style-type: none"> Does not relate to patients with Pompe disease

Abbreviations: EMBASE, Excerpta Medica database; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; TGA, Therapeutic Goods Administration

^a Search will be restricted from 2009 as ToR previously not seen by LSDP

^b Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

In addition to the systematic literature review, PI for the LSDP subsidised Pompe disease medicine will be obtained from the TGA website. Dosage and administration information from the PI will be compared against the real-world use of medicines available in the LSDP dispensing dataset (refer to Section 7.4). This comparison will enable an analysis of how compliant LSDP patients are to treatment to inform research questions 8 and 9 as well as identification of treatment breaks to inform research question 10. Information from the LSDP eligibility criteria for Pompe disease will be used to address research question 5. Finally, information from the Presentation and Storage Conditions section of the PI will be used to describe the intended way the medication should be stored by medicine custodians and will inform research question 11.

7.3 LSDP PATIENT-LEVEL DATA

The LSDP patient-level dataset and dispensing dataset will be linked by a unique identifier for each patient. This will allow the examination of any relationship between changes in clinical variables and dosing. LSDP patient-level data will be used to understand reasons for any change in the use of the medicine. Reasons which may be identified through the analysis of the LSDP patient-level data may include disease progression, reduction in the clinical effectiveness of treatment, and adverse events. The level of antibodies to treatment and clinical indicators of disease severity may be included in clinical notes. Any additional information included in clinical notes will be analysed to address research questions 1 to 5 and 7 to 10 concerning patient compliance, and utilisation (including beyond progression).

7.4 LSDP DISPENSING DATA

Two variables in the LSDP dispensing dataset will be used to inform the research questions in ToR 6:

- (1) The number of days between dispensing will be used to inform research question 9. A mean, standard deviation, median, and inter-quartile range will be calculated to provide detail on the variability of the interval between dosing across the entire LSDP.

To inform research question 10, the interval between dosing will be compared with the dosage regimen from the literature.
- (2) The dispensed amount will be calculated using the vial strength and the number of vials dispensed on each occasion. Summary statistics will be produced for the dispensed amount. This will be compared with the prescribed dose, as well as product information to assess whether the actual use of the medicine complies with the approved use. This will also allow identification of any medication wastage and a breakdown of annual wastage costs. Identifying the amount of medicine patients receive, including whether patients are on treatment at all, will be used to address all ToR 6 research questions.

7.5 LSDP PRICING DATA

The unit costs from the LSDP pricing data will be used to calculate the cost of LSDP medicines dispensed over the period of funding. This will be compared to the financial projections at the time of listing to address research question 3 and the rate of change will be calculated to address research question 4. To calculate the amount of wastage and address research question 6, the total cost of the program will be compared with the amount which would be spent if exact quantities of the medicine could be dispensed. These wastage calculations will supplement the value for money calculations in ToR 5.

7.6 PBAC SUBMISSIONS

The estimated number of patients that will use the medicine, the unit costs, and the total cost of funding over five years will be extracted from the financial estimates in Section 4 of the relevant PBAC submissions. The number of patients and total cost of providing the medicine will be compared between the real-world costs (based on LSDP dispensing and pricing data) and the initial projections. It will be determined whether the difference between the two is due to a discrepancy in the total number of patients, the number of units of the medicine dispensed, or the unit cost of the medicine. Other than for direct comparison to the projections at the time of funding, the PBAC submissions may also give insight into the process of deciding upon criteria such as eligibility and maximum dosing. This data will be used to address research questions 1 to 6, and 8.

7.7 STAKEHOLDER CONSULTATION

Stakeholders may be approached to fill any information gaps identified within the utilisation assessment. This consultation may occur by approaching specific stakeholders directly or through administration of an online survey. Again, the use of expert opinion to address the research questions in the review will follow the methods described in Appendix A of the PBAC guidelines. The content of these questions will focus on the reasons for the utilisation behaviour observed in the dispensing data and any issues with compliance.

7.8 SYNTHESIS OF FINDINGS

To address the research questions related to utilisation (research questions 1 to 6), LSDP dispensing data and LSDP pricing data will be used to create a budget impact analysis calculating the number of patients on the LSDP medicine, the amount of medicine used in each year, the unit cost of each dose, and the total cost to the LSDP for each year. Actual costs using LSDP data will be compared to projected costs from the historical PBAC submission. To address research question 5, LSDP patient-level data and dispensing data will be interrogated to identify patients whose disease has progressed to the point where ERT is no longer a suitable treatment. Stakeholder input will be sought if the LSDP datasets are not sufficient for this purpose. The criteria which define whether a patient is no longer suitable for ERT will be based on the exclusion criteria from the Pompe disease guidelines. For research question 6 (wastage), real-world utilisation will be compared with the modelled situation where it is possible to dispense the exact required dosages.

To address the research questions related to compliance (research questions 7 to 10), LSDP dispensing data will be analysed to assess the duration of treatment, average dose and interval between dosing (including breaks from treatment). This will be compared to the PI in order to assess whether practice is compliant with the approved use of the medicine. The systematic literature review will be used to inform the findings on patient compliance to treatment and supplemented by qualitative data gathered through stakeholder consultation process. Analysis of stakeholder input will be used to inform the reasons for any dosing deviations.

To address drug storage, stakeholder input will be sought to determine how LSDP medicines are stored at various points between reception at the pharmacy and administration. Thematic analysis of the stakeholder input will be compared with directions on storage and handling from the PI. This will inform research question 11 by determining whether users are handling the medicine appropriately.

7.9 LIMITATIONS

The most significant limitation in ToR 6 is the quality of the LSDP datasets. ToR 6 involves in depth analysis of the LSDP patient-level and dispensing datasets to identify information which addresses the research questions. Any gaps in the data will impact the ability to inform and/or validate the data against each of the

research questions. For research question 5 (utilisation of medicines beyond the eligibility criteria) for example, it may not be possible to identify when disease progression has occurred from the LSDP patient level or dispensing data. It is also important to place suitable parameters to define treatment breaks in the analysis of patient compliance. Where analyses are unable to be conducted or there is a lack of confidence in the validity of the results due to data quality issues, this will be noted and suggestions will be made regarding how to address these issues at the system-level in the future.

ToR 7: Developing technologies that may impact future access

This Chapter outlines the methodology to address ToR 7 *“Investigate developing technologies that may impact future funded access.”*

The purpose of ToR 7 is to identify what treatments and/or testing methodologies, if any, are emerging for Pompe disease and what impact (if any) this could have on the administration of the program going forward.

8.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 7

To address ToR 7, a horizon scan of developing technologies and innovations that may impact future access (i.e. within the next five years) to the LSDP Pompe disease medicine will be undertaken. For the purpose of the scan, technologies are defined as emerging treatments and testing methodologies. Table 8.1 presents the research questions to address ToR 7 and the data sources which will be used to answer each of the research questions.

Table 8.1: Research questions to address ToR 7

ToR 7 research questions	Data sources						
	Peer-reviewed literature databases	Early assessment and alert systems	HTA / research organisations	Regulatory agencies	News	Clinical trials registries	Other sources ^a
1. What new treatments are emerging and how are they to be used?	+	+	+	+	+	+	+
2. What new patient testing methodologies are being developed / adopted / promoted?	+	+	+	+	+	+	+
3. What is the potential impact of developing technologies on the LSDP?	+	+	+	+	+	+	+

Abbreviations: HTA, health technology assessment; LSDP, Life Saving Drugs Program; ToR, term of reference

^a Includes Australian Pompe Association

Horizon scans are implemented to detect emerging healthcare technologies and innovations and inform stakeholders. Identified technologies and innovations undergo rapid assessment and are prioritised based on their potential impact for patients and the healthcare system. Consequently, these could impact on future access. Furthermore, identified technologies and innovations could have the ability to impact the administration of the LSDP. This could be due to the identification of extra patients, see more usage, thus, increasing government expenditure. Potentially significant technologies and innovations will be assessed in terms of their effectiveness, cost, safety, impact to the health system and ethical considerations.

The following sections explain how each of the identified data sources will be used to inform the analysis undertaken for each of the research questions.

8.2 PEER-REVIEWED LITERATURE

A search of the literature for new and emerging pharmaceuticals and testing methodologies relevant to Pompe disease will be conducted using:

- (1) Peer-reviewed databases: Cochrane, PubMed, and Embase.com. The PubMed search terms are provided in Table 8.2. The databases will be searched using Boolean logic and the syntax unique to each database.
- (2) The selected sources given in Appendix E will also be reviewed for new medicines or molecules for rare diseases and conditions. Further detail on the systematic review methodology is in Appendix B.

Table 8.2: Literature search criteria for ToR 7

Parameter	Search terms and limits
Search terms	<ul style="list-style-type: none"> Synonyms for Pompe disease and an appropriate filter to identify clinical guidelines will guide the search. Details of the terms are provided in Section D.7 of Appendix D.
Limits	<ul style="list-style-type: none"> English and reputable trials not published in English AND humans
Search period	<ul style="list-style-type: none"> Articles published from 2015^a Conference abstracts published since 2017^b

^a Search will be restricted from 2015 to identify new and current treatment modalities

^b Conference abstracts/posters subject to a two-year restriction to allow for manuscript publication of current evidence

The sources shown in Table E-1 located in Appendix E (also summarised in Sections 8.3-8.8), will be searched using the same terms. However, searches will be varied using single terms, phrases, or combinations of these due to the search limitations that each source allows. A simpler approach is likely required for sources that use a search engine platform, although advanced searches will be used if the option is available. The horizon scan seeks to determine the impact of technologies and innovations that are likely to emerge within the next five years. Given the lag time in regulatory submissions between Europe, American and Australia, the horizon scan will search for papers from 2015 (or abstracts from 2017) to account for this.

8.3 EARLY ASSESSMENT AND ALERT SYSTEMS

Three different sources that specialise in scanning for future treatments will be utilised as described in Appendix E. By using these sources, incoming technologies can be detected and analysed for their potential impact on future access and usage of Pompe disease treatments. By using three different sources it is believed that information will likely be corroborated or further supported, allowing for better analysis. Additionally, by using multiple sources, exclusive findings and publications can also be detected.

8.4 HTA/INDEPENDENT RESEARCH ORGANISATIONS

Several different HTA agencies and research organisations will also be sourced to determine the impact of impending technologies on future access as described in Appendix E. Given the nature of these organisations, emerging technologies will have gone through an assessment with their impact assessed for a foreign healthcare system. However, the benefits of novel technologies are likely to be identified and communicated in their publications. These findings will also be used in assessing for the impact of developing technologies on future access of Pompe disease treatments.

8.5 REGULATORY AGENCIES

Three main agencies (EMA, FDA and TGA) will also be reviewed. By researching these agencies, technologies that are likely to be commercially available in Australia within the next five years can also be

identified. From the reports obtained, information such as efficacy and safety data can also be presented to inform the impact of developing technologies on future access for Pompe disease patients.

8.6 NEWS

News websites specialising in healthcare, pharmaceutical and testing technologies will be researched for any developing innovations as described in Appendix E. Furthermore, other commercially available products that could impact Pompe disease patients but may not necessarily go through the traditional regulatory and HTA route can also be identified. The potential impact of new innovations on Pompe disease patient numbers, usage of medications and government expenditure will also be analysed. Lastly, news websites can also be used to corroborate on findings from other data sources but also report on exclusive news.

8.7 CLINICAL TRIAL DATABASES

Four main clinical trial registries will be reviewed to identify developing technologies that could impact future access for Pompe disease patients as described in Appendix E. These databases will be used to identify novel therapeutic agents that may be submitted to a regulatory agency as well as an HTA agency. Clinical trial databases will also identify developing technologies from Phase I to IV but also provide a synopsis on the type of technology used.

8.8 OTHER

Other resources, as described in Appendix E, will also be investigated. This is not only corroborate findings from the other five major sources but also identify any other missing pieces of information that could impact on the assessment of developing technologies on future access of Pompe disease treatments.

Also, stakeholders consulted as part of the other ToRs, will be asked whether they are aware of any new treatments and/or patient testing methodologies, and what impact if any, they believe they will have on the LSDP over the next five years.

8.9 SYNTHESIS OF FINDINGS

Identified developing health technologies will be presented according to their category (e.g. treatment or test). Categories of findings will be discussed, with detail provided for new technologies. Where possible, the likelihood of emergence of the new technology in the near future will be assessed. Particular types of new and emerging technologies will be reviewed briefly in which the following will be included:

- Introduction (Brief background)
- Intervention (What is the technology? How does it work?)
- Comparators (What other options are available?)
- Where will the intervention fit in the management algorithm for Pompe disease?
- What are the characteristics of the population in whom it is being studied?
- Effectiveness (How well does the technology reach its outcomes?)
- Safety
- Cost impact
- Ethical cultural or religious considerations
- List of studies/references

In addition to these criteria, a summary sheet will be completed (Appendix E, Table E-2). The goal of the summary sheet is to provide a synopsis of the identified technology, in addition to its clinical and regulatory progress to date. The table will also address the other criteria listed above where possible.

By addressing these topics, the identified technology's impact on: a patient's life expectancy; quality of life; whether alternative treatments are available; and the Australian health system can be reviewed. Technologies to emerge within the next three years will be presented and discussed. Any medicines that are not expected to emerge within this time frame (e.g. medicines for which only animal studies are available) will not be reviewed.

- 1 Australian Government. Department of Health. *Acronyms and Glossary*. 2017; Available from: <http://www.health.gov.au/internet/main/publishing.nsf/content/glossary>.
- 2 (NIH), N.I.o.H. *Pompe Disease Registry*. 2019 15 April 2019]; Available from: <https://clinicaltrials.gov/ct2/show/NCT00231400?term=registry+OR+survey&cond=Pompe+Disease&rank=1>
- 3 van der Meijden C. Post-marketing experiences in Pompe disease 2016;
- 4 Van der Meijden, J., Güngör, D., Kruijsaar, M., Muir, A., Broekgaarden, H., and Van Der Ploeg, A. Ten years of the international Pompe survey: patient reported outcomes as a reliable tool for studying treated and untreated children and adults with non-classic Pompe disease. *Journal of inherited metabolic disease* 2015; 38(3): 495-503
- 5 Australian Government. The Pharmaceutical Benefits Advisory Committee (PBAC). Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee. *Journal* 2016;
- 6 New York State Department of Health. Newborn Screening for Pompe Disease Information for Parents
- 7 Australian Government. Department of Health. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee. Version 5.0. *Journal* 2016;
- 8 Australian Government. Department of Health. Life Saving Drugs Program (LSDP) guidelines for initial application and annual reapplication for subsidised treatment for Pompe disease. 2018;
- 9 Australian Commission on Safety and Quality in Health Care. *Patient-Reported Outcome Measures*. 2018; Available from: <https://www.safetyandquality.gov.au/our-work/indicators/patient-reported-outcome-measures/>.
- 10 Rothrock, N.E., Kaiser, K.A., and Cella, D. Developing a valid patient-reported outcome measure. *Clin Pharmacol Ther* 2011; 90(5): 737-42
- 11 Deshpande, P.R., Rajan, S., Sudeepthi, B.L., and Abdul Nazir, C.P. Patient-reported outcomes: A new era in clinical research. *Perspect Clin Res* 2011; 2(4): 137-44
- 12 Canadian Agency for Drugs and Technologies in Health (CADTH). *Strings Attached: CADTH's Database Search Filters*. 2016 21 January 2019]; Available from: <https://www.cadth.ca/resources/finding-evidence/strings-attached-cadth-database-search-filters#guide>.
- 13 Australian Government. Department of Health. Manual of resource items and their associated unit costs. Version 5.0. *Journal* 2016;
- 14 Australian Government. Department of Health. Life Saving Drugs Program (LSDP) guidelines for initial and annual reapplication for subsidised treatment for Pompe disease (Type 1). 2018;
- 15 Australian Pompe Association (APA). *Diagnosis*. 2017 15 April 2019]; Available from: <http://australianpompe.org.au/find-out-more/diagnosis/>.
- 16 Genzyme Corporation. *RegistryNXT!* 2016 15 April 2019]; Available from: <https://www.registrynxt.com/>.
- 17 International Pompe Association. *Pompe Survey*. 2019 15 April 2019]; Available from: <https://www.worldpompe.org/index.php/pompe-disease/pompe-survey>.
- 18 Australian Pompe Association (APA). *Our Aim*. 2017 10 April 2019]; Available from: <http://australianpompe.org.au/about-australian-pompe-association/our-aim/>.
- 19 Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., and Group, P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151(4): 264-9, W64

- 20 Coleman, K., Norris, S., Weston, A., Grimmer-Somers, K., Hillier, S., Merlin, T., and Tooher, R.J.C.N. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. 2005;
- 21 Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., and Kristjansson, E.J.b. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. 2017; 358(j4008
- 22 Guyatt, G., Oxman, A.D., Akl, E.A., Kunz, R., Vist, G., Brozek, J., Norris, S., Falck-Ytter, Y., Glasziou, P., and Jaeschke, R.J.J.o.c.e. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. 2011; 64(4): 383-394
- 23 Balshem, H., Helfand, M., Schünemann, H.J., Oxman, A.D., Kunz, R., Brozek, J., Vist, G.E., Falck-Ytter, Y., Meerpohl, J., and Norris, S.J.J.o.c.e. GRADE guidelines: 3. Rating the quality of evidence. 2011; 64(4): 401-406
- 24 Consortium, A.N.S. *The AGREE II Instrument [Electronic version]*. 2017 24 January 2019]; Available from: <https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf>
- 25 Higgins, J., Sterne, J., Savović, J., Page, M., and Hróbjartsson, A.J.C.D.o.S.R. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). *Cochrane Methods*. 2016; 10(
- 26 Online Mendelian Inheritance in Man (OMIM). # 232300 *GLYCOGEN STORAGE DISEASE II; GSD2*. 2014 11 April 2019]; Available from: <https://www.omim.org/entry/232300>.
- 27 American Association of Neuromuscular & Electrodiagnostic Medicine. CONSENSUS TREATMENT RECOMMENDATIONS FOR LATE-ONSET POMPE DISEASE. 2011;
- 28 Disorders, N.O.f.R. *Pompe Disease*. 2017 10 April 2019]; Available from: <https://rarediseases.org/rare-diseases/pompe-disease/>.
- 29 Barba-Romero, M.A., Barrot, E., Bautista-Lorite, J., Gutierrez-Rivas, E., Illa, I., Jimenez, L.M., Ley-Martos, M., Lopez de Munain, A., Pardo, J., and Pascual-Pascual, S.I. Clinical guidelines for late-onset Pompe disease. *Rev Neurol* 2012; 54(8): 497-507
- 30 Kronn, D.F., Day-Salvatore, D., Hwu, W.-L., Jones, S.A., Nakamura, K., Okuyama, T., Swoboda, K.J., Kishnani, P.S., and Group, P.D.N.S.W. Management of confirmed newborn-screened patients with Pompe disease across the disease spectrum. *Pediatrics* 2017; 140(Supplement 1): S24-S45
- 31 American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM). Late-Onset' Pompe Disease Presentation, Diagnosis, and Management A CME Monograph
- 32 Lysosomal Diseases New Zealand (LDNZ). *POMPE DISEASE (GLYCOGEN STORAGE DISEASE)*. 11 April 2019]; Available from: http://www.ldnz.org.nz/lysosomal_diseases/list_of_lyosomal_disorders/pompe_disease_glycogen_storage_disease.
- 33 Moravej, H., Amirhakimi, A., Showraki, A., Amoozgar, H., Hadipour, Z., and Nikfar, G. A New Mutation Causing Severe Infantile-Onset Pompe Disease Responsive to Enzyme Replacement Therapy. *Iranian journal of medical sciences* 2018; 43(2): 218
- 34 Kishnani, P.S., Steiner, R.D., Bali, D., Berger, K., Byrne, B.J., Case, L.E., Crowley, J.F., Downs, S., Howell, R.R., and Kravitz, R.M. Pompe disease diagnosis and management guideline. *Genetics in Medicine* 2006; 8(5): 267
- 35 Burton, B.K., Kronn, D.F., Hwu, W.-L., Kishnani, P.S., and Group, P.D.N.S.W. The initial evaluation of patients after positive newborn screening: recommended algorithms leading to a confirmed diagnosis of Pompe disease. *Pediatrics* 2017; 140(Supplement 1): S14-S23
- 36 Toscano, A., Montagnese, F., and Musumeci, O. Early is better? A new algorithm for early diagnosis in late onset Pompe disease (LOPD). *Acta Myologica* 2013; 32(2): 78
- 37 Australian Government. Myozyme Product Information. 2016

APPENDIX A: DESCRIPTION OF DATA SOURCES

A.1 LSDP PATIENT-LEVEL DATA

LSDP patient-level data is collected annually for all patients on the LSDP through the initial and annual reapplication for LSDP subsidised treatment for Pompe disease.

Through the LSDP, the Australian Government provides subsidised access for eligible patients to expensive lifesaving medicines. Treating physicians with relevant specialist registration who wish to apply for their patients to receive access to Australian Government subsidised treatment for Pompe disease through the LSDP are required to complete criteria for general, initial and ongoing eligibility to access subsidised treatment.

The treating physician must submit the reapplication form to the LSDP by 1 May every year if they wish their patients to continue to receive subsidised treatment through the LSDP.

The reapplication form must demonstrate clinical improvement in the patient or stabilisation of the patient's condition, and evidence to support ongoing eligibility for the treatment of Pompe disease must be provided.

The treating physician must declare that the patient continues to meet the eligibility criteria to receive subsidised treatment through the LSDP in accordance with the guidelines.

For Pompe disease, a patient must:

- (1) satisfy the initial and ongoing eligibility criteria as detailed below;
- (2) participate in the evaluation of effectiveness of the drug by periodic assessment, as directed by these Guidelines, or have an acceptable reason not to participate;
- (3) not be suffering from any other medical condition, including complications or sequelae of Pompe disease, that might compromise the effectiveness of the drug treatment; and
- (4) be an Australian citizen or permanent Australian resident who qualifies for Medicare.¹⁴

LSDP patient-level data collected annually for patients on the LSDP receiving Pompe disease treatment (alglucosidase alfa) are presented in Table A-1 for infantile-onset,

Table A-2 for juvenile-late onset and Table A-3 for adult-late onset Pompe disease.

Table A-1: LSDP data collected annually from Infantile onset Pompe disease patients

LSDP patient-level data
Demographics
Height (incremental percentile)
Weight (incremental percentile)
BMI (kg/m ²) (incremental percentile)
Head Circumference (incremental percentile)
Haematological
Enzyme Activity - Acid Alpha glucosidase activity (mmol / hr / mg protein)
Haemoglobin (g/L)
Platelets (g/L)
Creatinine Kinase
Alanine Amino Transferase (ALT)
Aspartate Amino Transferase (AST)
Lactate Dehydrogenase (LDH)
Urine Tetrasaccharide (Glc 4)
Second Diagnostic Test (if not urine Glc 4)
CRIM Status
Mutation Analysis
Antibody levels (Titre Value)
IgG
IgE
Sleep Study
Number/hour
Lowest saturation
Number of desaturations <80%
Apnoea Hypopnoea Index
Respiratory
Ventilatory Support (degree of support)
Chest X-ray
Cardiology
Echocardiogram (date). Include rating on New York Heart Association Functional Class
Ejection fraction (%)
Fraction Shortening (%)
Left ventricle hypertrophy (thickness)
Valvular Pathology
Valvular stenosis/regurgitation (grade)
Electrocardiography
24-hour ECG - (Holter): Optional
Paediatric Cardiology assessment
Cerebral MRI (Ultrasound until able to have MRI without anaesthetic): Optional
Psychometric Testing
Developmental Testing: As required
Gross Motor Function Measure (GMF)
Swallowing assessment
Audiology
Full neurological Assessment
Reflexes
RUL
LUL
RLL
LRL
Tone
RUL
LUL
RLL

LSDP patient-level data
LLL
Power(?/5)
RUL
LUL
RLL
LLL
Plantar
RLL
LLL
History of other illness, co-morbidities, diagnoses
Current Medication
Other Medical Problems

Source: Australian Government. Department of Health. Accessed 2019. Saving Drugs Program (LSDP) guidelines for initial and annual reapplication for subsidised treatment for Pompe disease

Abbreviations: ALT, alanine amino transferase; AST, aspartate amino transferase; CRIM, cross-reactive immunological material; ECG, electrocardiogram; Glc4, glucose tetrasaccharide; GMF, gross motor function; Ig, immunoglobulin; kg, kilogram; LDH, lactate dehydrogenase; LLL, left lower limb; LUL, left upper limb; m, meters; MRI, Magnetic resonance imaging; RLL, right lower limb; RUL, right upper limb

Table A-2: LSDP data collected annually from Juvenile late onset pompe disease patients

LSDP patient-level data
Demographics
Height (incremental percentile)
Weight (incremental percentile)
Haematological
Enzyme Activity - Acid Alpha glucosidase activity (mmol / hr / mg protein)
Urine Tetrasaccharide (Glc 4)
Mutation Analysis
Sleep Study
Number/hour
Lowest saturation
Number of desaturations <80%
Apnoea Hypopnoea Index
Respiratory
Ventilatory Support (degree of support)
6-Minute walk test (6MWT) distance (m)
Forced Vital Capacity (FVC)
Forced Expiratory Volume in 1 second (FEV 1)
% of Predicted Forced Vital Capacity
% of Predicted Forced Expiratory Volume in 1 second
History of other illness, co-morbidities, diagnoses
Current Medication

Source: Australian Government. Department of Health. Accessed 2019. Saving Drugs Program (LSDP) guidelines for initial and annual reapplication for subsidised treatment for Pompe disease

Abbreviations: 6MWT, 6-minute walk test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; Glc4, glucose tetrasaccharide; m, metre

Table A-3: LSDP data collected annually from Adult late onset pompe disease patients

LSDP patient-level data
Demographics
Height (incremental percentile)
Weight (incremental percentile)
Haematological
Enzyme Activity - Acid Alpha glucosidase activity (mmol / hr / mg protein)
Urine Tetrasaccharide (Glc 4)
Mutation Analysis
Sleep Study
Number/hour
Lowest saturation
Number of desaturations <80%
Apnoea Hypopnoea Index
Respiratory
Ventilatory Support (degree of support)
6-Minute walk test (6MWT) distance (m)
Forced Vital Capacity (FVC)
% of Predicted Forced Vital Capacity
History of other illness, co-morbidities, diagnoses
Current Medication

Source: Australian Government. Department of Health. Accessed 2019. Saving Drugs Program (LSDP) guidelines for initial and annual reapplication for subsidised treatment for Pompe disease

Abbreviations: 6MWT, 6-minute walk test; FVC, forced vital capacity; Glc4, glucose tetrasaccharide; m, metre

A.2 LSDP DISPENSING DATA

LSDP dispensing data is collected continuously throughout the year for all patients on the LSDP receiving subsidised access to medications.

A pharmacist who is nominated by the treating physician to receive and dispense LSDP medications is designated as an 'Authorised Person' and has a range of responsibilities regarding the LSDP stock. These

responsibilities include receiving the stock, confirming that it is in good condition, ensuring that the stock is handled in accordance with the TGA approved product information, checking the expiry date, and notifying the Department if the patient is enrolled in a clinical trial or has ceased treatment.

A major responsibility is that pharmacists are required to maintain a dispensing record for each patient. This record is based on a template provided by the Department and if a dispensing record is not provided when requested, the Department is unable to place an order for that particular patient. The Department audits these details approximately every three months to review patient compliance and determine future supply requirements.

The information included in these dispensing records for patients on the LSDP receiving Pompe disease treatment with alglucosidase alfa is presented in Table A-4.

Table A-4: LSDP dispensing data collected from Pompe disease patients

LSDP Dispensing Data	
Identifying information	
Patient identifier (e.g. X01)	
Date of birth	
Age	
Month on the program	
Year on the program	
Dispensing information	
Date of dispensing	
Date of infusion	
Number of days between dispensing	
Prescribed dose	
Dispensed amount (50mg vial)	
Dispensed amount – compassionate use (50mg vial)	
Dispensed amount (mg)	
Amount discarded (mg)	
Cost of discarded amount	
Dispensing pharmacy	
Comments	

Source: Australian Government Department of Health. Accessed 2019. Life Saving Drugs Program (LSDP) Pompe dispensing records.

A.3 LSDP PRICING DATA

The LSDP pricing data includes details on the arrangement between the Department and the pharmaceutical company that own the medication for Pompe disease. The data collected regarding the pricing of LSDP medications is presented in Table A-5.

Table A-5: LSDP pricing data for Pompe disease medications

LSDP Pricing Data	
General information	
Medicine (i.e. alglucosidase alfa)	
Date of funding	
Sponsor	
Deed expiry date	
Number of patients	
Average patient age	
Average dose	
Number of new applications in 2017-2018	
Number of doctors	
Pricing	
Price per vial (GST ex)	

LSDP Pricing Data

Price per vial after 1 April 2019

Annual average cost per patient for 2017-2018

Source: Australian Government Department of Health Life. Accessed 2019. Life Saving Drugs Program (LSDP) Attachment A (1) Brief overview of Pompe disease treated through the LSDP

A.4 PBAC SUBMISSIONS

All medicines on the LSDP have undergone assessment by the PBAC, but been rejected because of failure to meet the required cost-effectiveness criteria. These submissions will include both clinical effectiveness and safety clinical evaluation. The economic information, includes:

- type of economic evaluation
- comparator
- estimated number of patients with the disease (and by onset type)
- estimated number of patients that will take the medicine

A.5 SPECIALIST LABORATORY DATA

Diagnosis of Pompe disease is done by measuring acid alpha-glucosidase enzyme activity in the blood. Pompe disease patient samples are delivered as a dried blood spot on a paper card. It is processed at one national diagnostic lab:¹⁵

(1) National Referral Laboratory, Department of Biochemical Genetics, Women's and Children's Hospital, SA
Stakeholders also advised that PathWest may also conduct some of the testing. This will be further investigated. HealthConsult will be consulting with this site to retrieve de-identified diagnostic laboratory datasets that may be used to inform questions raised in the Review.

A.6 RARE DISEASE REGISTRIES

Rare disease registries are typically run by international pharmaceutical companies, such as Sanofi Genzyme. These registries hold observational data for monitoring and evaluating patient outcomes in response to treatment specific to their condition. HealthConsult will be seeking access to Australian data held within de-identified patient registry databases to collect and analyse any information that may be relevant to the Review.

The databases of particular interest for the current Review include:

- Pompe Disease Registry (via RegistryNxt)¹⁶: <https://www.registrynxt.com/>
- IPA/Erasmus¹⁷: <https://www.worldpompe.org/index.php/pompe-disease/pompe-survey>

The International Pompe Association (IPA) along with Erasmus medical centre in Rotterdam Netherlands registry is called "the survey" and has partnered with Sanofi Genzyme. European POMpe Consortium (EPOC) covers ~1,250 Pompe disease patients across 11 European countries. However it is unlikely this consortium would hold Australian patient data.³

A.7 AUSTRALIAN POMPE ASSOCIATION

The Australian Pompe Association is a non-profit association with the aim to:¹⁸

- communicate information relating to Pompe disease treatment and glycogen storage disease
- establish a responsible body for local and international parties to receive advice on new therapies

- increase participation by members in treatment and clinical trials for Pompe disease medicines
- establishing support groups
- represent patients to local and international pharmaceutical companies
- provide representation to the Australian Medical Association and the Department of Health for access to medications
- be a charitable foundation, raise funds, support members and ensure the Association is sustainable.

Australian Pompe Association input will be sought where the data source “Stakeholder Consultation” is included in a ToR.

Appendix B: SYSTEMATIC LITERATURE REVIEW METHODOLOGY

B.1 SYSTEMATIC LITERATURE SEARCH

A systematic literature review is a rigorous and highly methodical appraisal and synthesis of research articles.¹⁹ HealthConsult will conduct systematic reviews in three steps:

- (1) **Identification of relevant evidence** – The identification of evidence relevant to all ToR will rely on a systematic literature review. The search strategies will encompass both the peer reviewed literature and any additional evidence (such as, published international registry data and public summary documents or unpublished PBAC pivotal trial data) provided by key stakeholders.

The Medline, EMBASE and Cochrane Library databases will be searched for eligible peer-reviewed articles. These will include clinical studies that consider the medicines alglucosidase alfa (Myozyme [also known as Lumizyme in the US]) for the treatment of Pompe disease without neurological complications. Restrictions will be placed on the time period searched, from 2009 for ToR 1 (prevalence) and ToR 6 (utilisation) and 2012 for the rest of the ToR to capture evidence that has not previously been included/considered by the LSDP. The reference lists of relevant papers will also be scanned for other studies potentially missed in the database searches.

All eligible articles will be downloaded into EndNote (X 9). Two reviewers from the evidence review team will independently screen titles and abstracts (where available) for all citations retrieved by the literature search. All citations listed for inclusion for full text review will be independently assessed by the two independent reviewers. Any disagreements will be resolved by a third reviewer to reach consensus.

The 'a priori' inclusion criteria will be determined from the PICO criteria that form the basis of the research question. Studies reporting at least one primary outcome will be eligible for inclusion if they satisfied the correct population, intervention and comparator criteria. Outcomes of interest to be reported are relevant life extension, primary efficacy and safety outcomes (e.g. cardiac outcomes, degree of ventilatory support, forced vital capacity etc). Exclusion criteria include literature identified as opinion pieces, editorials or other papers without a clear study design or description of methods or results or low powered statistical results. It also includes literature included in the 2015 LSDP review report.

Eligibility criteria will be applied to the titles and abstracts of included citations; full articles will be retrieved for further assessment where the citation appears to meet the eligibility criteria. The same criteria will be applied to the full articles. Full articles that initially met the eligibility criteria but which were later excluded will be documented, with reasons for exclusion reported. Study eligibility will be assessed by two reviewers from the evidence review team who will screen titles and abstracts (where available) for all citations retrieved by the literature search. All citations listed for inclusion for full text review will be assessed by the same independent reviewers. Any disagreements will be resolved by a third reviewer.

Studies will be assessed for eligibility for inclusion in the systematic review using a staged approach; that is, the highest level of evidence available to answer the individual research questions will be included in the systematic review. The level of evidence will be determined by the NHMRC Evidence Hierarchy for interventional evidence, as described in Appendix C.2. The use of a staged approach targets the research most likely to provide unbiased evidence as a consequence of how the research was designed. However, other factors, such as study quality, size of the treatment effect, generalisability and applicability of the evidence, will also be considered when assessing the reliability of study findings.

The flow of information through the different phases of the systematic literature review will be presented in a Preferred Reporting of Items in Systematic Reviews and Meta-analyses (PRISMA) flow diagram.¹⁹ Studies that initially met inclusion criteria but were later excluded will be documented, with reasons for their exclusion.

- (2) **Critical Appraisal of selected evidence** – Studies will be critically appraised according to the likelihood that bias had affected their findings. Study design flaws will be appraised using NHMRC levels of evidence (Appendix B.2).²⁰ Systematic reviews will be critically appraised using the AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) checklist (Appendix C).²¹ The execution of RCTs and observational studies will be evaluated using quality appraisal checklists from Cochrane Risk of Bias for RCTs and ROBINS – 1 (Risk Of Bias In Non-randomised Studies - of Interventions) (see Appendix B.3). Case reports will not be assessed due to their likelihood of bias.

The quality of the body of evidence reported on individual health outcomes will be rated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.²² The GRADE system classifies the overall quality/level of the body of evidence for each outcome into one of four scores:²³

- (1) **High:** we are very confident that the true effect lies close to that of the estimate of the effect.
- (2) **Moderate:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- (3) **Low:** our confidence in the effect estimate is limited: the true effect maybe substantially different from the estimate of the effect.
- (4) **Very low:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Systematic reviews are considered to provide the strongest evidence if they summarise one or more well-designed and well-executed RCTs and yield consistent and directly applicable results. In the GRADE methodology, systematic reviews and RCTs both start as high-quality evidence. However, review authors can downgrade RCTs to moderate, low, or even very low quality evidence, depending on the presence of one or more of the following factors: limitations in the design and implementation of available studies suggesting high likelihood of bias; unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); indirectness of evidence (indirect population, intervention, control, outcomes); imprecision of results (wide confidence intervals); and high probability of publication bias.

The moderate strength category is populated by RCTs with important limitations; observational studies are generally graded as low-quality evidence. If, however, these studies yield large effects and there is no obvious bias explaining those effects, reviewers may rate the evidence as moderate or – if the effect is large enough – even high quality.

- (3) **Data extraction** – Relevant data will be extracted from included studies, including study design characteristics, country/setting, main population characteristics (including baseline characteristics or disease severity, if available), intervention drug and dosage details, comparator drug and dosage details, level of evidence, risk of bias, relevant outcome measures and results, and follow-up period. All data extraction will be cross-checked by a second reviewer.

Where appropriate, data extracted from the included studies will be combined in a meta-analysis, using Review Manager software from the Cochrane Collaboration. For each research question, the findings will be synthesised into an overall narrative, with better quality studies given greater weight in the formulation of conclusions. Where there is incomplete reporting of information in published systematic reviews, data will be verified using the original papers. The synthesis of the evidence will be informed by the GRADE method.²²

B.2 LEVELS OF EVIDENCE

When identifying clinical evidence, a stepped process will generally be used in which the highest-level evidence will be assessed for inclusion before lower levels of evidence will be considered. If there is sufficient Level I evidence to address the ToR (and research questions), assessment of Level II, III and IV evidence will not be undertaken. If no relevant Level I evidence is available for a particular research question, Level II evidence will be assessed. If no relevant Level II evidence is available these steps will be repeated for lower levels of evidence. Table B-1 describes the NHMRC Levels of Evidence for intervention questions.

Table B-1: NHMRC evidence hierarchy for intervention questions

Level	Study type	Notes
I	A systematic review of level II studies	A systematic review will only be assigned a level of evidence as high as the studies it contains
II	A randomised controlled trial	-
III-1	A pseudo-randomised controlled trial	-
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> Non-randomised experimental trial Cohort study Case-control study Interrupted time series with a control group 	Non-randomised experimental trial also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A v B and B v C to determine A v C)
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> Historical control study Two or more single arm study Interrupted time series without a parallel control group 	A comparison of single arm studies could involve case series from two studies. This would also include unadjusted indirect comparisons (utilise A v B and B v C to determine A v C, but where there is no statistical adjusted for B)
IV	Case series with either post-test or pre-test/post-test outcomes	-

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: National Health and Medical Research Council, 2009.

B.3 QUALITY ASSESSMENT

B.3.1 Clinical treatment guidelines

Clinical treatment guidelines will be assessed using the AGREE II (Appraisal of Guidelines for Research and Evaluation II) checklist²⁴ consisting of 23 items (See Table B-2). AGREE II allows for appraisers to make two final assessments of their overall judgement of the methodological quality of practice guidelines. This is made in consideration of how they rated the 23 items. Two appraisers will be used when evaluating the quality of outcomes.

The AGREE II guidelines are divided into six major quality domains:

- (1) Scope and purpose;
- (2) Stakeholder involvement;
- (3) Rigour of development;
- (4) Clarity of presentation;
- (5) Applicability; and
- (6) Editorial independence.

AGREE II items are rated out of 7, with a score of 1 being “Strongly Disagree,” and a score of 7 being “Strongly Agree.” A score between 2 and 6 is given when the AGREE II item does not fully meet the criteria or considerations. Scores are assigned based on completeness of data.

Table B-2: Quality assessment checklist for clinical guidelines

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.	<input type="checkbox"/> Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) <input type="checkbox"/> Expected benefit(s) or outcome(s) <input type="checkbox"/> Target(s) (e.g., patient population, society)	
2. QUESTIONS Report the health question(s) covered by the guideline, particularly for the key recommendations.	<input type="checkbox"/> Target population <input type="checkbox"/> Intervention(s) or exposure(s) <input type="checkbox"/> Comparisons (if appropriate) <input type="checkbox"/> Outcome(s) <input type="checkbox"/> Health care setting or context	
3. POPULATION Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.	<input type="checkbox"/> Target population, sex and age <input type="checkbox"/> Clinical condition (if relevant) <input type="checkbox"/> Severity/stage of disease (if relevant) <input type="checkbox"/> Comorbidities (if relevant) <input type="checkbox"/> Excluded populations (if relevant)	
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.	<input type="checkbox"/> Name of participant <input type="checkbox"/> Discipline/content expertise (e.g., neurosurgeon, methodologist) <input type="checkbox"/> Institution (e.g., St. Peter's hospital) <input type="checkbox"/> Geographical location (e.g., Seattle, WA) <input type="checkbox"/> A description of the member's role in the guideline development group	
5. TARGET POPULATION PREFERENCES AND VIEWS Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.	<input type="checkbox"/> Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) <input type="checkbox"/> Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) <input type="checkbox"/> Outcomes/information gathered on patient/public information <input type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS Report the target (or intended) users of the guideline.	<input type="checkbox"/> The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) <input type="checkbox"/> How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS Report details of the strategy used to search for evidence.	<input type="checkbox"/> Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) <input type="checkbox"/> Time periods searched (e.g., January 1, 2004 to March 31, 2008) <input type="checkbox"/> Search terms used (e.g., text words, indexing terms, subheadings) <input type="checkbox"/> Full search strategy included (e.g., possibly located in appendix)	
8. EVIDENCE SELECTION CRITERIA Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.	<input type="checkbox"/> Target population (patient, public, etc.) characteristics <input type="checkbox"/> Study design <input type="checkbox"/> Comparisons (if relevant) <input type="checkbox"/> Outcomes <input type="checkbox"/> Language (if relevant) <input type="checkbox"/> Context (if relevant)	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE #
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.	<input type="checkbox"/> Study design(s) included in body of evidence <input type="checkbox"/> Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) <input type="checkbox"/> Appropriateness/relevance of primary and secondary outcomes considered <input type="checkbox"/> Consistency of results across studies <input type="checkbox"/> Direction of results across studies <input type="checkbox"/> Magnitude of benefit versus magnitude of harm <input type="checkbox"/> Applicability to practice context	
10. FORMULATION OF RECOMMENDATIONS Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.	<input type="checkbox"/> Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) <input type="checkbox"/> Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) <input type="checkbox"/> How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	
11. CONSIDERATION OF BENEFITS AND HARMS Report the health benefits, side effects, and risks that were considered when formulating the recommendations.	<input type="checkbox"/> Supporting data and report of benefits <input type="checkbox"/> Supporting data and report of harms/side effects/risks <input type="checkbox"/> Reporting of the balance/trade-off between benefits and harms/side effects/risks <input type="checkbox"/> Recommendations reflect considerations of both benefits and harms/side effects/risks	
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE Describe the explicit link between the recommendations and the evidence on which they are based.	<input type="checkbox"/> How the guideline development group linked and used the evidence to inform recommendations <input type="checkbox"/> Link between each recommendation and key evidence (text description and/or reference list) <input type="checkbox"/> Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	
13. EXTERNAL REVIEW Report the methodology used to conduct the external review.	<input type="checkbox"/> Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) <input type="checkbox"/> Methods taken to undertake the external review (e.g., rating scale, open-ended questions) <input type="checkbox"/> Description of the external reviewers (e.g., number, type of reviewers, affiliations) <input type="checkbox"/> Outcomes/information gathered from the external review (e.g., summary of key findings) <input type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE Describe the procedure for updating the guideline.	<input type="checkbox"/> A statement that the guideline will be updated <input type="checkbox"/> Explicit time interval or explicit criteria to guide decisions about when an update will occur <input type="checkbox"/> Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.	<input type="checkbox"/> A statement of the recommended action <input type="checkbox"/> Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) <input type="checkbox"/> Relevant population (e.g., patients, public) <input type="checkbox"/> Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) <input type="checkbox"/> If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE #
16. MANAGEMENT OPTIONS Describe the different options for managing the condition or health issue.	<input type="checkbox"/> Description of management options <input type="checkbox"/> Population or clinical situation most appropriate to each option	
17. IDENTIFIABLE KEY RECOMMENDATIONS Present the key recommendations so that they are easy to identify.	<input type="checkbox"/> Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms <input type="checkbox"/> Specific recommendations grouped together in one section	
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION Describe the facilitators and barriers to the guideline's application.	<input type="checkbox"/> Types of facilitators and barriers that were considered <input type="checkbox"/> Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) <input type="checkbox"/> Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) <input type="checkbox"/> How the information influenced the guideline development process and/or formation of the recommendations	
19. IMPLEMENTATION ADVICE/TOOLS Provide advice and/or tools on how the recommendations can be applied in practice.	<input type="checkbox"/> Additional materials to support the implementation of the guideline in practice. For example: <ul style="list-style-type: none"> ○ Guideline summary documents ○ Links to check lists, algorithms ○ Links to how-to manuals ○ Solutions linked to barrier analysis (see Item 18) ○ Tools to capitalize on guideline facilitators (see Item 18) ○ Outcome of pilot test and lessons learned 	
20. RESOURCE IMPLICATIONS Describe any potential resource implications of applying the recommendations.	<input type="checkbox"/> Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) <input type="checkbox"/> Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) <input type="checkbox"/> Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) <input type="checkbox"/> How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.	<input type="checkbox"/> Criteria to assess guideline implementation or adherence to recommendations <input type="checkbox"/> Criteria for assessing impact of implementing the recommendations <input type="checkbox"/> Advice on the frequency and interval of measurement <input type="checkbox"/> Operational definitions of how the criteria should be measured	
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY Report the funding body's influence on the content of the guideline.	<input type="checkbox"/> The name of the funding body or source of funding (or explicit statement of no funding) <input type="checkbox"/> A statement that the funding body did not influence the content of the guideline	
23. COMPETING INTERESTS Provide an explicit statement that all group members have declared whether they have any competing interests.	<input type="checkbox"/> Types of competing interests considered <input type="checkbox"/> Methods by which potential competing interests were sought <input type="checkbox"/> A description of the competing interests <input type="checkbox"/> How the competing interests influenced the guideline process and development of recommendations	

Source: Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L, for the AGREE Next Steps Consortium. AGREE II: Advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010;182:E839-842.

B.3.2 Systematic Reviews

Systematic reviews will be assessed using the AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) checklist,²¹ which has 16 questions (see Table B-3). AMSTAR 2 enables appraisal of systematic reviews of randomised and non-randomised studies of healthcare interventions. AMSTAR 2 is not intended to generate an overall score. The overall rating is based on weaknesses in critical domains. The possible ratings of overall confidence in the results of the review are:

- **High** - Zero or one non-critical weakness: The systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- **Moderate** - More than one non-critical weakness*: The systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.
- **Low** - One critical flaw with or without non-critical weaknesses: The review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question(s) of interest.
- **Critically low** - More than one critical flaw with or without non-critical weaknesses: The review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

*Note: Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Table B-3 presents the AMSTAR 2 tool, a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions.

Table B-3: Quality assessment checklist for systematic reviews

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
1. Did the research question and inclusion criteria for the review include the components of PICO?		
For Yes: <input type="checkbox"/> Population <input type="checkbox"/> Intervention <input type="checkbox"/> Comparator group <input type="checkbox"/> Outcome	Optional (recommended) <input type="checkbox"/> Timeframe for follow-up	<input type="checkbox"/> Yes <input type="checkbox"/> No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: <input type="checkbox"/> review question(s) <input type="checkbox"/> a search strategy <input type="checkbox"/> inclusion/exclusion criteria <input type="checkbox"/> a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: <input type="checkbox"/> a meta-analysis/synthesis plan, if appropriate, and <input type="checkbox"/> a plan for investigating causes of heterogeneity <input type="checkbox"/> justification for any deviations from the protocol	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
For Yes, the review should satisfy ONE of the following: <input type="checkbox"/> <i>Explanation for including only RCTs</i> <input type="checkbox"/> OR <i>Explanation for including only NRSI</i> <input type="checkbox"/> OR <i>Explanation for including both RCTs and NRSI</i>		<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): <input type="checkbox"/> searched at least 2 databases (relevant to research question) <input type="checkbox"/> provided key word and/or search strategy <input type="checkbox"/> justified publication restrictions (e.g. language)	For Yes, should also have (all the following): <input type="checkbox"/> searched the reference lists/bibliographies of included studies <input type="checkbox"/> searched trial/study registries <input type="checkbox"/> included/consulted content experts in the field <input type="checkbox"/> where relevant, searched for grey literature <input type="checkbox"/> conducted search within 24 months of completion of the review	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: <input type="checkbox"/> at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include <input type="checkbox"/> OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer		<input type="checkbox"/> Yes <input type="checkbox"/> No
6. Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: <input type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies <input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer		<input type="checkbox"/> Yes <input type="checkbox"/> No
7. Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: <input type="checkbox"/> provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: <input type="checkbox"/> justified the exclusion from the review of each potentially relevant study	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No
8. Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): <input type="checkbox"/> described population <input type="checkbox"/> described interventions <input type="checkbox"/> described comparators <input type="checkbox"/> described outcomes <input type="checkbox"/> described research designs	For Yes, should also have ALL the following: <input type="checkbox"/> described population in detail <input type="checkbox"/> described interventions in detail (including doses where relevant) <input type="checkbox"/> described comparators in detail (including doses where relevant) <input type="checkbox"/> described study's setting <input type="checkbox"/> timeframe for follow-up	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs For Partial Yes, must have assessed RoB from: <input type="checkbox"/> unconcealed allocation, <i>and</i> <input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: <input type="checkbox"/> allocation sequence that was not truly random, <i>and</i> <input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No <input type="checkbox"/> Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: <input type="checkbox"/> from confounding, <i>and</i> <input type="checkbox"/> from selection bias	For Yes, must also have assessed RoB: <input type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i> <input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome	<input type="checkbox"/> Yes <input type="checkbox"/> Partial Yes <input type="checkbox"/> No <input type="checkbox"/> Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes: <input type="checkbox"/> must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies		<input type="checkbox"/> Yes <input type="checkbox"/> No
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11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs For Yes: <input type="checkbox"/> the authors justified combining the data in a meta-analysis <input type="checkbox"/> AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present <input type="checkbox"/> AND investigated the causes of any heterogeneity		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> No meta-analysis conducted
For NRSI For Yes: <input type="checkbox"/> the authors justified combining the data in a meta-analysis <input type="checkbox"/> AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present <input type="checkbox"/> AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available <input type="checkbox"/> AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
For Yes: <input type="checkbox"/> included only low risk of bias RCTs <input type="checkbox"/> OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?		
For Yes: <input type="checkbox"/> included only low risk of bias RCTs <input type="checkbox"/> OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results		<input type="checkbox"/> Yes <input type="checkbox"/> No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?		
For Yes: <input type="checkbox"/> There was no significant heterogeneity in the results <input type="checkbox"/> OR if heterogeneity was present, the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review		<input type="checkbox"/> Yes <input type="checkbox"/> No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?		
For Yes: <input type="checkbox"/> performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?		
For Yes: <input type="checkbox"/> The authors reported no competing interests OR <input type="checkbox"/> The authors described their funding sources and how they managed potential conflicts of interest		<input type="checkbox"/> Yes <input type="checkbox"/> No

Source: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008.

B.3.3 Randomised Controlled Trials (RCTs)

Quality appraisal checklists from the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)²⁵ will be used to assess the quality of RCTs (Table B-4). The RoB 2 tool provides a framework for considering the risk of bias in the findings of any type of randomized trial. The assessment is specific to a single trial result that is an estimate of the relative effect of two interventions or intervention strategies on a particular outcome. We refer to the interventions as the experimental intervention and the comparator intervention, although we recognise that the result may sometimes refer to a comparison of two active interventions.

The RoB 2 tool is structured into five domains through which bias might be introduced into the result. These are:

- (1) bias arising from the randomisation process;
- (2) bias due to deviations from intended interventions;

- (3) bias due to missing outcome data;
- (4) bias in measurement of the outcome;
- (5) bias in selection of the reported result.

The domain names are direct descriptions of the causes of bias addressed in the domain.

Table B-4: Quality assessment checklist for randomised controlled trials (Cochrane RoB 2)

Domain 1: Risk of bias arising from the randomization process		
Signalling Questions	Description	Response options
1.1 Was the allocation sequence random?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.3. If <u>Y</u> / <u>PY</u> / <u>NI</u> to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.4. If <u>Y</u> / <u>PY</u> to 2.3: Were these deviations from intended intervention balanced between groups?		NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.5 If <u>N</u> / <u>PN</u> / <u>NI</u> to 2.4: Were these deviations likely to have affected the outcome?		NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.7 If <u>N</u> / <u>PN</u> / <u>NI</u> to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)		
Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.3. If <u>Y</u> / <u>PY</u> / <u>NI</u> to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?		NA / <u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.4. Could failures in implementing the intervention have affected the outcome?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
2.5. Did study participants adhere to the assigned intervention regimen?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI

2.6. If N/PN/NI to 2.3 or 2.5 or Y/PY/NI to 2.4: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / <u>Y / PY</u> / <u>PN / N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Domain 3: Missing outcome data		
Signalling questions	Description	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		<u>Y / PY</u> / <u>PN / N</u> / NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?		NA / <u>Y / PY</u> / <u>PN / N</u>
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / <u>Y / PY</u> / <u>PN / N</u> / NI
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?		NA / <u>Y / PY</u> / <u>PN / N</u> / NI
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / <u>Y / PY</u> / <u>PN / N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Domain 4: Risk of bias in measurement of the outcome		
Signalling questions	Description	Response options
4.1 Was the method of measuring the outcome inappropriate?		<u>Y / PY</u> / <u>PN / N</u> / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		<u>Y / PY</u> / <u>PN / N</u> / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		<u>Y / PY</u> / <u>PN / N</u> / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / <u>Y / PY</u> / <u>PN / N</u> / NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / <u>Y / PY</u> / <u>PN / N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Domain 5: Risk of bias in selection of the reported result		
Signalling questions	Description	Response options
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?		<u>Y / PY</u> / <u>PN / N</u> / NI

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
5.3 ... multiple analyses of the data?		<u>Y</u> / <u>PY</u> / <u>PN</u> / <u>N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Overall risk of bias		
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Source: Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne on behalf of the ROB2 Development Group. Accessed 9 October 2018 <https://sites.google.com/site/riskofbiastool/>

Abbreviations: Y, Yes; PY, Probably yes; PN, Probably no; N, No; NI, No information

Notes: Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

The response options for an overall risk-of-bias judgement are the same as for individual domains. Reaching an overall risk-of-bias judgement for a specific outcome is presented in Table B-5 below.

Table B-5: Quality assessment checklist for randomised controlled trials (RoB 2)

Reaching an overall risk-of-bias judgement for a specific outcome.	
Overall risk-of-bias judgement	Criteria
Low risk of bias	The study is judged to be at low risk of bias for all domains for this result.
Some concerns	The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at high risk of bias in at least one domain for this result. Or The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Source: Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne on behalf of the ROB2 Development Group. 9 October 2018 <https://sites.google.com/site/riskofbiastool/>

B.3.4 Non-randomised trials

ROBINS-I tool ("Risk of Bias in Non-randomized Studies - of Interventions") is concerned with evaluating the risk of bias in the results of nonrandomized studies of the effects of interventions (NRSIs) that compare the health effects of two or more interventions (Table B-6). The types of NRSIs that can be evaluated using this tool are quantitative studies estimating the effectiveness (harm or benefit) of an intervention, which did not use randomization to allocate units (individuals or clusters of individuals) to comparison groups. This includes studies where allocation occurs during the course of usual treatment decisions or peoples' choices: such studies are often called "observational". There are many types of such NRSIs, including cohort studies, case-control studies, controlled before-and-after studies, interrupted time-series studies and controlled trials in which intervention groups are allocated using a method that falls short of full randomization (sometimes called "quasi-randomized" studies).

Table B-6: Quality assessment checklist for cohort studies (ROBINS -1)

Bias domain	Signalling questions	Response options
Bias due to confounding		
	1.1 Is there potential for confounding of the effect of intervention in this study? If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Y / PY / PN / N
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:	
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received? If N/PN , answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY , go to question 1.3.	NA / Y / PY / PN / N / NI
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N/PN , answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY , answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	NA / Y / PY / PN / N / NI
Questions relating to baseline confounding only		
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	NA / Y / PY / PN / N / NI
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI
	1.6. Did the authors control for any post- intervention variables that could have been affected by the intervention?	NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding		
	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	NA / Y / PY / PN / N / NI
	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA / Y / PY / PN / N / NI
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to confounding?	Favours experimental / Favours comparator / Unpredictable
Bias in selection of participants into the study		
	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of Intervention? If N/PN to 2.1: go to 2.4	Y / PY / PN / N / NI
	2.2. If Y/PY to 2.1: Were the post- intervention variables that influenced selection likely to be associated with intervention?	NA / Y / PY / PN / N / NI
	2.3 If Y/PY to 2.2: Were the post intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA / Y / PY / PN / N / NI
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Y / PY / PN / N / NI
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA / Y / PY / PN / N / NI

Bias domain	Signalling questions	Response options
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in classification of interventions		
	3.1 Were intervention groups clearly defined?	Y / PY / PN / N / NI
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y / PY / PN / N / NI
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Y / PY / PN / N / NI
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias due to deviations from intended interventions		
	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2	
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Y / PY / PN / N / NI
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA / Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6	
	4.3. Were important co-interventions balanced across intervention groups?	Y / PY / PN / N / NI
	4.4. Was the intervention implemented successfully for most participants?	Y / PY / PN / N / NI
	4.5. Did study participants adhere to the assigned intervention regimen?	Y / PY / PN / N / NI
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	NA / Y / PY / PN / N / NI
	Risk of bias judgement	
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?	
Bias due to missing data		
	5.1 Were outcome data available for all, or nearly all, participants?	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Y / PY / PN / N / NI
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NA / Y / PY / PN / N / NI
	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NA / Y / PY / PN / N / NI
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI

Bias domain	Signalling questions	Response options
	Optional: What is the predicted direction of bias due to missing data?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in measurement of outcomes		
	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y / PY / PN / N / NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Y / PY / PN / N / NI
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in selection of the reported result		
	Is the reported effect estimate likely to be selected, on the basis of the results, from... 7.1. ... multiple outcome <i>measurements</i> within the outcome domain?	Y / PY / PN / N / NI
	7.2 ... multiple <i>analyses</i> of the intervention-outcome relationship?	Y / PY / PN / N / NI
	7.3 ... different <i>subgroups</i> ?	Y / PY / PN / N / NI
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI
	Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Overall bias		
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI
	Optional: What is the overall predicted direction of bias for this outcome?	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

Source: Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ* 2016; 355: i4919; doi: 10.1136/bmj.i4919.

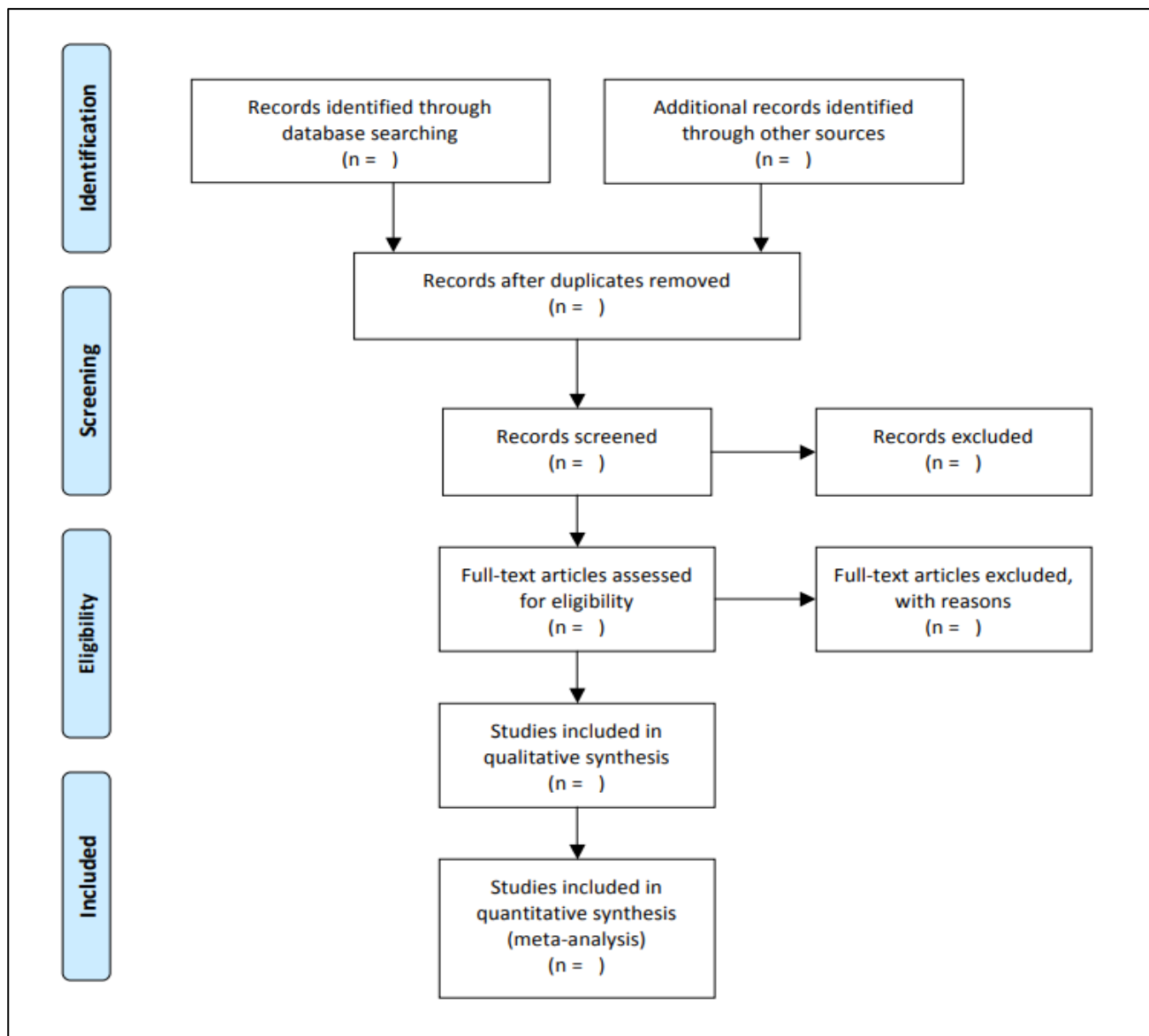
Abbreviations: Y, Yes; PY, Probably yes; PN, Probably no; N, No; NI, No information

Notes: Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

B.4 PRISMA FLOW DIAGRAM

The flow of information through the different phases of the systematic literature review will be presented in a PRISMA Flow Diagram. Figure B-1 presents a PRISMA flow chart for systematic review.

Figure B-1: PRISMA flow chart for systematic review



Source: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and MetaAnalyses: The PRISMA Statement. PLoS Med 6(7)

APPENDIX C: POMPE DISEASE IN AUSTRALIA

This Appendix provides a brief description of Pompe disease and how it is diagnosed and managed.

C.1 DESCRIPTION AND DIAGNOSIS OF POMPE DISEASE

Pompe disease is an autosomal recessive genetic disorder and is the prototypic lysosomal storage disease²⁶. The underlying pathology is a deficiency of the enzyme acid alpha-glucosidase (GAA) that hydrolyses lysosomal glycogen. Approximately 500 different GAA gene variations have been identified, although not all are pathogenic.^{27, 28} The α -glucosidase gene is located on the long arm of chromosome 17 (17q25.2-q25.3).

Pompe disease is characterised by the steady accumulation of glycogen in tissues (primarily muscular) which can lead to increased weakness, organ failure and ultimately death. Severity varies according to the age of onset, rate of progression of organ involvement and muscle involvement.²⁹ Table C-1 presents a comparison of common characteristics of infantile-onset and late-onset (juvenile/adult) Pompe disease.

Infantile onset Pompe disease can be characterised by the classic and non-classic types. Infantile onset Pompe disease tends to be the most severe type. For patients with the classic type, the onset of symptoms tends to occur within the first year of life and include: cardiomegaly, generalised muscle weakness, hypotonia, hepatomegaly and death from respiratory failure before the end of the first year of life. Although the clinical presentation of classic infantile-onset Pompe disease is quite homogeneous.^{29, 30}

The non-classic form usually appears by the age of one. It is characterised by delayed motor skills (such as rolling over and sitting) and progressive muscle weakness. The heart may be abnormally large (cardiomegaly), but affected patients usually do not experience heart failure. The muscle weakness leads to serious breathing problems, and most children with non-classic infantile-onset Pompe disease live only into early childhood.²⁸

The late-onset type of Pompe disease may not become apparent until later in childhood, adolescence, or adulthood. It can present as early as after the age of one to as late as 60+.³¹ Late-onset Pompe disease is usually milder than the infantile-onset forms of this disorder and is less likely to involve the heart. Childhood and adult Pompe disease are associated with progressive weakness of mainly the proximal muscles (limb girdle- upper arms and upper legs), and varying degrees of respiratory impairment due to dysfunction of the diaphragm and intercostal muscles. In the late-onset form, respiratory complications can often lead to severe clinical repercussions such as respiratory failure.

In the late-onset form, the lower limbs are more affected than the upper limbs, although, the extent of muscle involvement is highly variable. The muscles adjacent to the spinal column and neck are usually also affected. Weakness of the para-spinal muscles around puberty can also cause abnormal curvature of the spine (scoliosis). Consequently, as a result of the combination of these serious symptoms, affected individuals may become wheelchair and/or ventilator dependent.

Other symptoms can include chewing and swallowing difficulties and drooping of the upper eyelids (ptosis). Additionally, blood vessel abnormalities due to smooth muscle weakness and problems of the urinary and digestive systems have been reported.^{28, 29, 31}

The different forms of Pompe disease are generally correlated with α -glucosidase activity, which in affected infants under the age of one is usually less than 1% of normal activity, while in the juvenile form it is less than 10% and in adults less than 40%²⁹. Furthermore, life expectancy by onset type varies³²:

- Life expectancy for the classic infantile Pompe Disease is two years of age or younger, resulting from respiratory or cardiac failure.
- Life expectancy for the non-classic infantile Pompe Disease is early childhood.

- Life expectancy for the juvenile form Pompe Disease is 30 years of age or younger.
- Life expectancy for the adult form Pompe Disease is 50 years of age or younger

Table C-1: Comparison of Characteristics Associated With Infantile-Onset and Late-Onset Pompe Disease

Feature	Infantile-Onset Pompe Disease	Late-Onset Pompe Disease
Onset	First year of life (typically first few months of life)	>1 year to adulthood
GAA enzyme activity	Typically absent	Some residual activity
Cardiomyopathy	Present and often severe (e.g. cardiac failure, disturbances of rhythm, cardiomegaly, cardiomyopathy)	Typically not present; some cases of WPW syndrome reported
Common signs and symptoms at presentation	Hypotonia, profound muscle weakness, respiratory insufficiency/distress, respiratory infections, and feeding difficulties/failure to thrive are among the most common symptoms. Hepatomegaly Macroglossia	Musculoskeletal symptoms (e.g. mobility problems, limb-girdle weakness, back pain, rigid spine syndrome, muscle cramps) Respiratory symptoms (e.g. frequent respiratory infections, respiratory distress or insufficiency, sleep-disordered breathing, oxygen desaturation when supine) Gastrointestinal symptoms (e.g. difficulties eating/swallowing, poor weight gain in children)
Rate of progression	Rapid	Widely variable, slower than for the infantile-onset form
Death	Typically occurs within the first year of life Often caused by cardiorespiratory failure or respiratory infection	Age of death varies - childhood to late adulthood Respiratory failure is the most common cause of death Death as a result of cerebral aneurysm has been reported

Source: American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) *Late-Onset Pompe Disease: Presentation, Diagnosis, and Management A Continuing Medical Education Monograph*. Table 1 p6³¹.

Abbreviations: GAA, acid α-glucosidase; WPW, Wolff-Parkinson-White.

The most common mutation found in late-onset patients is the c.-32-13T>G mutation, which is seen in one allele in approximately 60% of patients with late-onset Pompe disease. This gene is also most common in Caucasians.^{31, 33} Other reported pathogenic variants are presented in Table C-2.

Table C-2: Reported proportion of patients with selected GAA pathogenic variants

GAA Pathogenic Variant	Pompe disease subtype	% of affected Individuals	Ethnic group/population
p.Glu176ArgfsTer45	Infantile onset	34%	Dutch
	Infantile onset	9%	US
p.Gly828_Asn882del	Infantile onset	25%	Dutch
	Infantile onset	25%	Canadian
	Infantile onset	5%	US
c.336-13T>G	Late onset	36%-90%	Italian
p.Asp645Glu	Infantile onset	≤80%	Taiwanese & Chinese
p.Arg854Ter	Infantile onset	≤60%	African

Source: Centogene 2019, *Glycogen Storage Disease II or Pompe Disease* accessible from: <https://www.centogene.com/science/centopedia/glycogen-storage-disease-ii-or-pompe-disease.html>

Abbreviations: GAA, acid α-glucosidase

C.2 ACCESS TO LSDP MEDICINES FOR PATIENTS WITH POMPE DISEASE

The LSDP subsidises the full cost of one medication used to treat patients with Pompe disease. For patients over six years of age 6MWT, FVC, and Forced Expiratory Volume in one second (FEV₁) results using a standardised protocol is requested. Formal respiratory review is required for adult late-onset Pompe disease.⁸ Patients need to satisfy the criteria set out in Table C-3 to be eligible for LSDP subsidies.

Table C-3: LSDP Guidelines on patient eligibility criteria

Overarching criteria for all patients	Criteria for initial application	Criteria for ongoing treatment	Exclusions criteria
<ul style="list-style-type: none"> • Patient is a permanent Australian resident who qualifies for Medicare. • Patient is not suffering from other medical condition, including complications or sequelae of Infantile-onset, Juvenile Late onset or Adult Late-onset Pompe disease that might compromise effectiveness of LSDP drug under application. • Patient meets the initial and ongoing criteria outlined in LSDP Guidelines (detailed below) for individual disease-specific medicines listed on the LSDP. 	<p>(a) Diagnosis of Pompe disease using one of two documented methods:</p> <ul style="list-style-type: none"> • deficiency of acid alpha-glucosidase by prenatal diagnosis using chorionic villus biopsies and/or cultured amniotic cells; <p style="text-align: center;">OR</p> <ul style="list-style-type: none"> • At least two of the following confirmatory diagnostic tests from a NATA accredited laboratory: <ul style="list-style-type: none"> i) Documented deficiency of acid alpha-glucosidase in dried blood spot or lymphocytes or mixed leukocytes or skin fibroblasts or skeletal muscle. ii) Documented urinary tetrasaccharide testing indicating a diagnostic elevation of glucose tetrasaccharides. iii) Documented molecular genetic testing indicating a disease causing mutation in the acid alpha-glucosidase gene (GAA gene). <p>At the time of initial application the patient is aged up to 24 months and has a documented diagnosis of Infantile-onset Pompe disease; or</p> <p>At the time of initial application the patient is aged over 24 months and under 18 years and has a documented diagnosis of Juvenile Late-onset Pompe disease, or</p> <p>At the time of initial application the patient is aged 18 years or over and has a documented diagnosis of Adult Late-onset Pompe disease and the patient must present with at least one of the following treatment criteria*:</p> <ul style="list-style-type: none"> i) Respiratory Function Test. Patients with Forced Vital Capacity (FVC), either supine or erect, less than 80% of predicted value. Both supine and erect FVC should be performed. 	<p>Subsidised treatment may continue unless one or more of the following situations apply:</p> <ul style="list-style-type: none"> • failure to comply adequately with treatment or measures. • failure to provide data, copies of test results and the Excel spreadsheet for Infantile-onset, Juvenile Late-onset or Adult Late-onset Pompe disease, evidencing the effectiveness of the therapy; • therapy fails to relieve the symptoms of disease that originally resulted in the patient being approved for subsidised treatment; • evidence of disease progression despite regular therapy, • including but not limited to the development of the need for 24-hour invasive ventilation, for a period of fourteen days or greater, provided that: <ul style="list-style-type: none"> · the cardiorespiratory failure is progressive; · the requirement for ventilation is not due to a potentially reversible problem such as infection; and · muscle tone is so poor that there is no useful movement; • for Adult Late-onset Pompe patients a decline of 20% or greater versus prior year on measures of 6MWT* or a decline of 10% or greater versus prior year on measures of erect FVC. † • development of a life-threatening complication, which would compromise the effectiveness or 	<p>The following conditions render a patient ineligible for subsidised treatment of Pompe disease through the LSDP:</p> <ul style="list-style-type: none"> • Patients on long-term invasive ventilation for respiratory failure prior to starting enzyme replacement therapy (ERT) which indicates a disease severity that will not benefit from treatment (Patients requiring acute ventilation for conditions such as cardiac failure or acute respiratory infection should not be excluded). • Patients with the presence of another life threatening or severe disease where the prognosis is unlikely to be influenced by ERT. • Patients with the presence of another medical condition • that might reasonably be expected to compromise a response to ERT. • Current smokers.

Overarching criteria for all patients	Criteria for initial application	Criteria for ongoing treatment	Exclusions criteria
<ul style="list-style-type: none"> • Patient must participate in the evaluation of effectiveness of the drug by periodic assessment, as directed by the LSDP Guidelines, or have a reason not to participate. 	<p>ii) Sleep Disordered Breathing. Patients with an apnoea/hypopnoea incidence of >five events/hour of total sleep time or more than two severe episodes of desaturation (oxygen saturation <80%) in an overnight sleep study.</p> <p>iii) Significant muscular weakness. Patients with significant muscular weakness as evidenced by Manual Muscle Testing (MMT) (employing the MRC score) of four or less in either limb girdle accompanied by a 6 Minute Walk Test (6MWT).</p>	<p>benefit from continued ERT, including the patient has severe infusion related adverse reactions or antibody-related reactions which are not preventable or controlled by appropriate premedication and/or adjustment of infusion rates;</p> <ul style="list-style-type: none"> • the patient develops another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by ERT; or the patient develops another medical condition that might reasonably be expected to compromise a response to ERT. 	<p>Furthermore, patients participating in a clinical trial are not eligible for subsidised treatment through the LSDP. Previous involvement in a clinical trial does not impede eligibility to subsidised treatment through the LSDP.</p>

Source: Australian Government. Department of Health (2018) *LSDP - Information for patients, prescribers and pharmacists*⁹; Australian Government. Department of Health (2018) LSDP Life Saving Drugs Program (LSDP) guidelines for initial application and annual reapplication for subsidised treatment for Infantile-onset, Juvenile Late-onset or Adult Late-onset Pompe disease

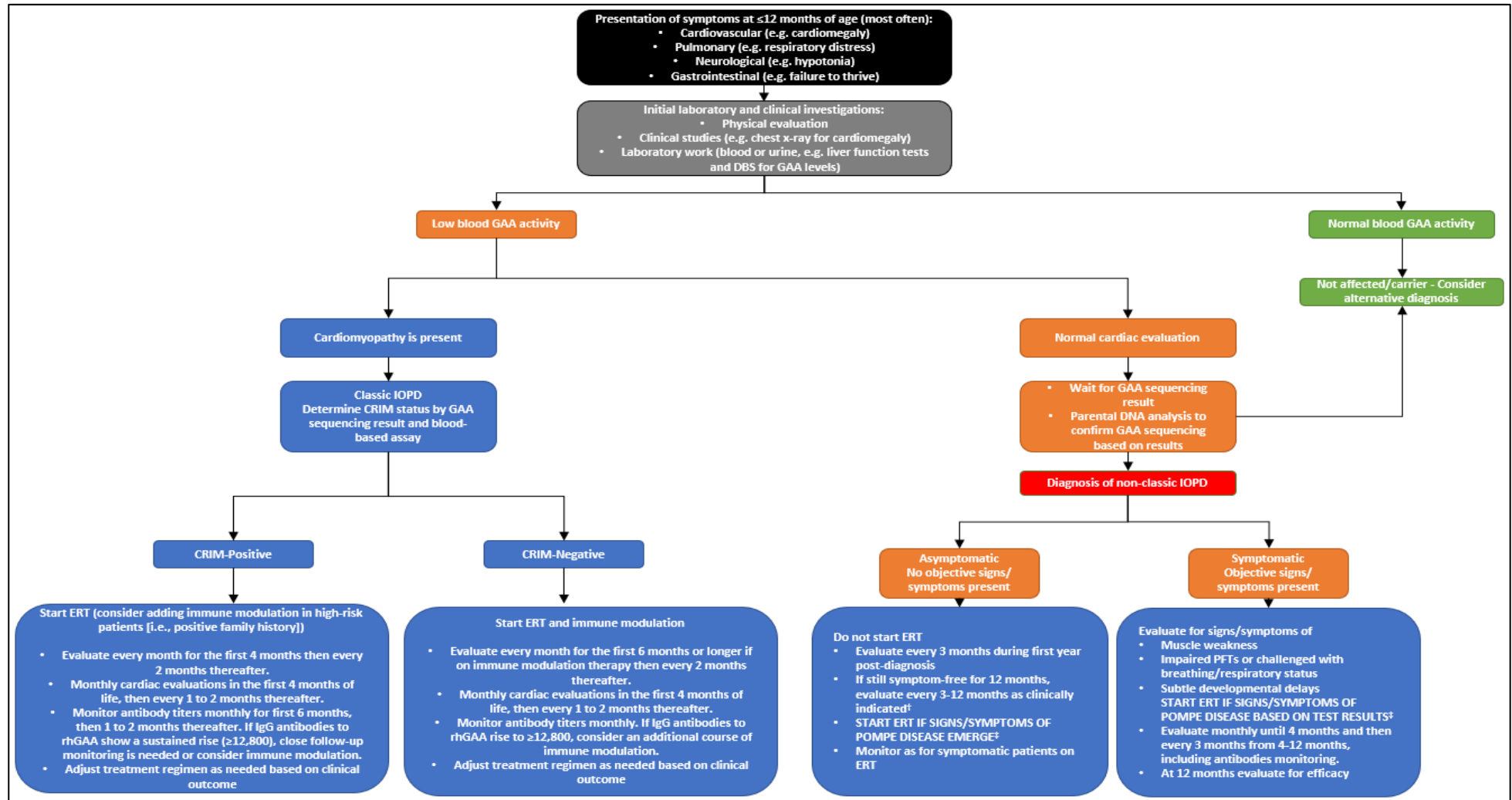
Note: **For patients receiving alglucosidase alfa (Myozyme®) before 1 September 2015 the requirement of fulfilling initial treatment criteria is not applied.

† To ensure consistency of testing, the test should be undertaken again within 3 months. Test results of 6MWT and FVC must be provided to LSDP at the first six months of initial treatment and thereafter annually. A review of the data to evaluate these parameters will commence 2 years after the initial subsidy was provided.

Figure C-1 provides a simple clinical treatment algorithm of how patients diagnosed with classic infantile onset Pompe disease obtain access to treatment. Figure C-2 demonstrates the algorithm for non-classic infantile onset and late onset populations (juvenile and adult onset) Pompe patients. Of note, non-classic infantile onset Pompe disease has been included in the infantile onset population. These patients typically have no measurable signs or symptoms, clinical manifestations, or predictable onset of symptoms at screening. Consequently, clinicians are faced with deciding when and if to start ERT.³⁰

More information on how the current guidelines determine access to Pompe disease medication can be found in Appendix C.2. Testing protocols and clinical results that are monitored as part of the LSDP can be found in Table A-1 of Appendix A.1.

Figure C-1: Clinical treatment algorithm for classic and non-classic infantile onset Pompe Disease



Source: Kishnani et al., 2006 Figure 1 p271³⁴; Burton et al., 2017 Figure 2 pS17³⁵; Kronn et al., 2017 pS31 Figure 1³⁰

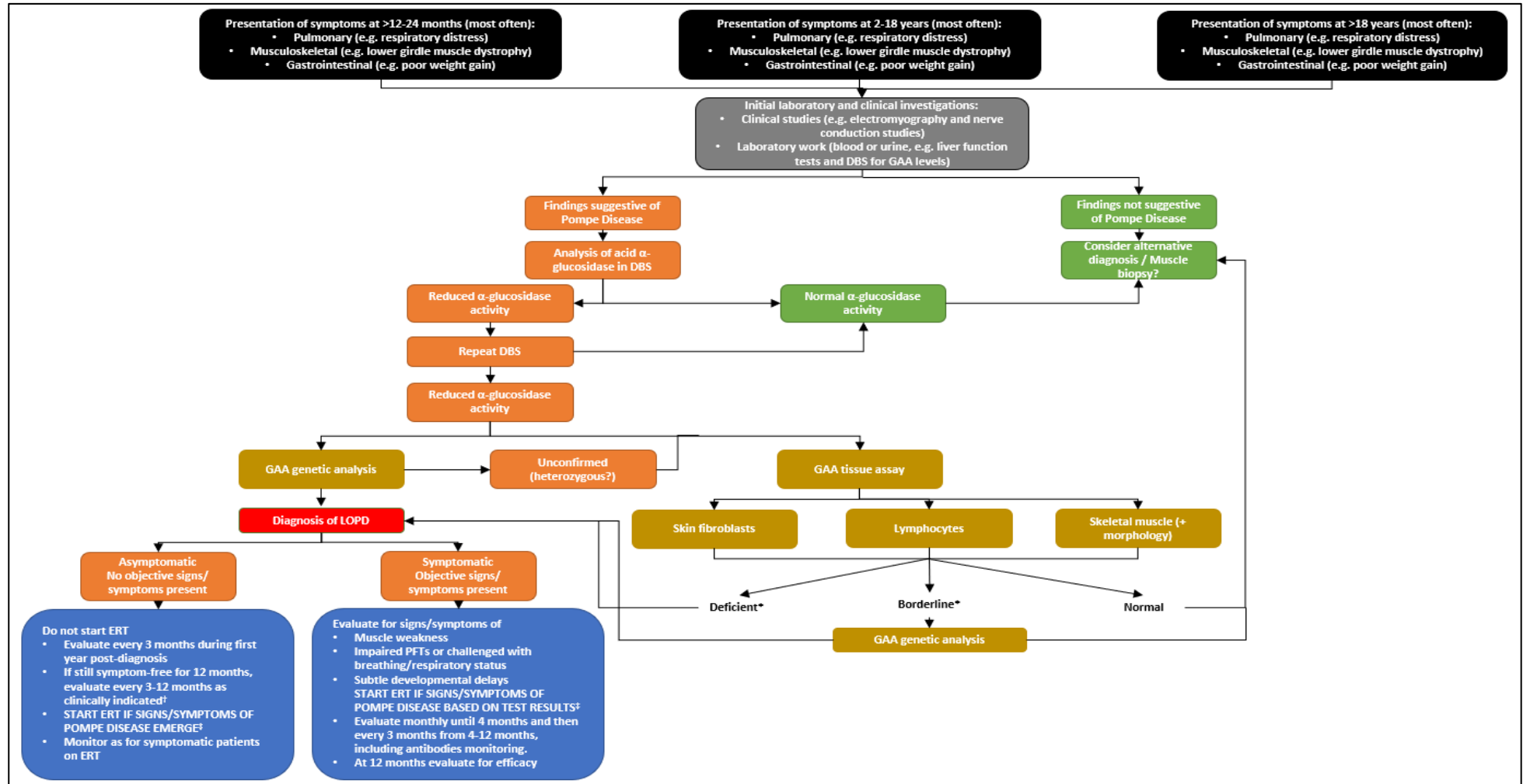
Abbreviations: CRIM, cross-reactive immunological material; DBS, dry blood spot; DNA, deoxyribonucleic acid; ERT, Enzyme reduction therapy; GAA, acid α-glucosidase; IgG, immunoglobulin G; IOPD, Infantile-onset Pompe Disease; rhGAA, recombinant human acid α-glucosidase

Note: The indicated dosage of ERT in Australia is 20mg/kg per fortnight

† If no concerns emerge and the patient remains clinically stable during the first 12 months, then evaluations can be spaced out accordingly, but are not to exceed 12-month intervals. If the results of evaluations raise questions or concerns, then closer follow-up will be needed. Parents of patients are asked to return if they have any concerns or questions of their own.

‡ Treatment decisions made after discussions between clinicians and individual patients and/or families

Figure C-2: Clinical treatment algorithm for late onset Pompe disease (i.e. juvenile and adult onset)



Source: Kishnani et al., 2006 Figure 2 p272³⁴; Barba-Romero et al., 2012 Figure 1 p502²⁹; Kronn et al., 2017 pS37 Figure 2³⁰; Toscano et al., 2013 p79 Figure 1³⁶

Abbreviations: CRIM, cross-reactive immunological material; DBS, dry blood spot; ERT, Enzyme reduction therapy; GAA, acid α-glucosidase; IgG, immunoglobulin G; LOPD, Late-onset Pompe Disease

Note:

The indicated dosage of ERT in Australian is 20mg/kg per fortnight

* GAA activity <30% qualifies as deficient, borderline is 30-40%.

† If no concerns emerge and the patient remains clinically stable during the first 12 months, then evaluations can be spaced out accordingly, but are not to exceed 12-month intervals. If the results of evaluations raise questions or concerns, then closer follow-up will be needed. Parents of patients are asked to return if they have any concerns or questions of their own.

‡ Treatment decisions made after discussions between clinicians and individual patients and/or families

C.3 PHARMACOLOGICAL MANAGEMENT OF POMPE DISEASE

In Australia, ERT has been the traditional approach to stabilising disease in Pompe patients. There is only one ERT option for long-term treatment of Pompe disease on the LSDP including:

- **Alglucosidase alfa (Myozyme®)**: a recombinant, purified form of the lysosomal enzyme, alfa-glucosidase (GAA), from the hamster-derived CHO cell line.³⁷ It has been available through the LSDP since 2010. A dosage of **20 mg/kg** of body weight by intravenous (IV) infusion over four hours every fortnight is currently indicated and recommended.

Concomitant pharmacological intervention is considered for some Pompe disease patients due to recurrent reactions. These consist of flu-like illness or a combination of events such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions. Symptoms usually last for a few days in some patients treated with alglucosidase alfa. Some patients have been observed to experience severe or significant hypersensitivity reactions, one of which is anaphylactic shock. The majority of patients are successfully rechallenged with alglucosidase alfa using lower doses and/or pre-treatment with anti-inflammatory drugs and/or corticosteroids and have continued to receive treatment under close clinical supervision.

Table C-4 summarises the only LSDP-funded medicine used for Pompe disease management including Pompe disease type, units/vial, date of listing and sponsor.

Table C-4: LSDP-subsidised ERT for the treatment of Pompe disease

Medicine	Units / vial	Date of listing	Sponsor
Alglucosidase alfa (Myozyme®) For infantile onset Pompe Disease	50mg / 10mL	1/02/2010	Genzyme
Alglucosidase alfa (Myozyme®) For juvenile onset Pompe Disease	50mg / 10mL	1/02/2015	Genzyme
Alglucosidase alfa (Myozyme®) For adult onset Pompe Disease	50mg / 10mL	1/09/2015	Genzyme

APPENDIX D: POTENTIAL SEARCH TERMS

D.1 POTENTIAL SEARCH TERMS: TOR 1

(< >) Strings to be placed inside (< >) include *infantile onset or juvenile late onset or adult late onset or left blank*.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase" OR "pseudodeficient") AND (Prevalence OR Epidemiology OR Incidence OR Morbidity OR "Allele frequency" OR "Mutation frequency" OR Cases OR Mortality OR Deaths OR Survival)

D.2 POTENTIAL SEARCH TERMS: TOR 2

CADTH's database of search filters¹² were consulted for this ToR. Below is the PubMed search string used for this ToR:

(< >) Strings to be placed inside (< >) include *infantile onset or juvenile late onset or adult late onset or left blank*.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase" OR "pseudodeficient") AND (Clinical pathway OR Clinical protocol OR Consensus OR Consensus development conferences as topic OR Critical pathways OR Guidelines as topic [Mesh:NoExp] OR Practice guidelines as topic OR Health planning guidelines OR guideline OR practice guideline OR consensus development conference OR consensus development conference OR position statement* OR policy statement* OR practice parameter* OR best practice* OR standards OR guideline* OR clinical algorithm* OR recommendat* OR screening OR examination OR assessment* OR test*) AND (Monitoring OR Outcomes OR "Follow up" OR "Disease severity")

D.3 POTENTIAL SEARCH TERMS: TOR 3

A comprehensive search of the scientific literature will be conducted to identify randomised controlled trials addressing the key research questions. Potential search terms for the identification of evidence relating to ToR 3, *alglucosidase alfa* to placebo within the database MEDLINE (via PUBMED.com) are shown in Table D-1. Syntax will be modified for database searches in EMBASE (via EMBASE.com), Cochrane Library (Includes the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Health Technology Assessment database), ClinicalTrials.gov, International Clinical Trials Registry Platform, Australian Clinical Trials Registry, Internal registries (e.g., Original PBAC funding application pivotal trials that informed the medicines inclusion on the LSDP) and other sources (e.g., Database of Adverse Events Notifications Data from ARTG, PBAC PSDs for Pompe disease, Product information documents for Pompe disease medicines on the ARTG, AIHW National Death Index data and Cause of Death data, Pompe disease registry and Pompe disease Outcome Survey published registry data reports).

Table D-1: Search terms for Medline (via PubMed) ToR 3, *alglucosidase alfa*, to placebo[#]

#	Search terms	Number of citations
#1	Randomized controlled trial [Publication Type]	480,766

#	Search terms	Number of citations
#2	Controlled clinical trial [Publication Type]	568,948
#3	Randomized [Title/Abstract]	476,027
#4	Placebo [Title/Abstract]	202,439
#5	Drug therapy [MeSH Subheading]	2,100,528
#6	Randomly [Title/Abstract]	309,753
#7	Trial [Title/Abstract]	544,516
#8	Groups [Title/Abstract]	1,929,846
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	4,482,301
#10	Animals [MeSH Terms] NOT Humans [MeSH Terms]	4,570,884
#11	#9 NOT #10	3,881,061
#12	Pompe [All Fields]	2,260
#13	Glycogen storage disease II [All Fields]	1,875
#14	Glycogen storage disease 2 [All Fields]	2,138
#15	GSD2 [All Fields]	8
#16	GSD II [All Fields]	1,887
#17	acid alpha-glucosidase deficiency [All Fields]	2,018
#18	GAA deficiency [All Fields]	2,055
#19	glycogenosis, generalized, cardiac form [All Fields]	85
#20	cardiomegalia glycogenica diffusa [All Fields]	0
#21	cardiomegalia glycogenica diffusa Schema: all	0
#22	acid maltase deficiency [All Fields]	1,980
#23	AMD [All Fields]	11,574
#24	Alpha-1,4-glucosidase deficiency [All Fields]	1,920
#25	Acid maltase [All Fields]	5,036
#26	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	19,702
#27	Infantile onset [All Fields]	4,590
#28	Juvenile late onset [All Fields]	801
#29	Adult late onset [All Fields]	22,129
#30	#26 AND #27	301
#31	#26 AND #28	39
#32	#26 AND #29	348
#33	Enzyme replac*[Text Word]	5,130
#34	Enzyme replacement therapy [MeSH Terms]	1,686
#35	#33 OR #34	5,130
#36	Alglucosidase alfa [All Fields]	307
#37	Myozyme OR lumizyme [All Fields]	278
#35	#36 OR #37	320
#36	#11 AND #26 AND #35	303 ^a
#37	#11 AND #26 AND #30	63 ^b
#38	#11 AND #26 AND #31	11 ^c
#39	#11 AND #26 AND #32	57 ^d

Abbreviations: AMD, acid maltase deficiency; GAA, acid alpha-glucosidase; GSD, glycogen storage disease; MeSH, medical subject headings;

Note: Date of search for reproducibility 17 Apr 2019

^a Search using Pompe disease without infantile onset or juvenile late onset or adult late onset

^b Search for infantile onset Pompe disease only

^c Search for juvenile late onset Pompe disease only

^d Search for adult late onset Pompe disease only

D.4 POTENTIAL SEARCH TERMS: TOR 4

(< >) Strings to be placed inside (< >) include infantile onset or juvenile late onset or adult late onset or left blank.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase") AND ("patient centred outcome" OR "patient centered outcome" OR "patient reported outcome" OR "patient related outcome" OR "patient outcome")

D.5 POTENTIAL SEARCH TERMS: TOR 5

For the search of economic evaluations:

(< >) Strings to be placed inside (< >) include infantile onset or juvenile late onset or adult late onset or left blank.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase")

AND

(Economics[Mesh:NoExp] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab])

For the search of quality of life:

Strings to be placed inside (< >) include infantile onset or juvenile late onset or adult late onset or left blank.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase")

AND

("Value of Life"[mh] OR Quality of Life[mh] OR quality of life[tiab] OR Quality-Adjusted Life Years[mh] OR quality adjusted life[tiab] OR qaly*[tiab] OR qald*[tiab] OR qale*[tiab] OR qtime*[tiab] OR life year[tiab] OR life years[tiab] OR disability adjusted life[tiab] OR daly*[tiab] OR sf36[tiab] OR sf 36[tiab] OR short form 36[tiab] OR shortform 36[tiab] OR short form36[tiab] OR shortform36[tiab] OR sf6[tiab] OR sf 6[tiab] OR short form 6[tiab] OR sf6d[tiab] OR sf 6d[tiab] OR short form 6d[tiab] OR sf8[tiab] OR sf 8[tiab] OR short form 8[tiab] OR sf12[tiab] OR sf 12[tiab] OR short form 12[tiab] OR sf16[tiab] OR sf 16[tiab] OR sf20[tiab] OR sf 20[tiab] OR short form 20[tiab] OR hq[tiab] OR hqol[tiab] OR h qol[tiab] OR hrqol[tiab] OR hr qol[tiab] OR hye[tiab] OR hyes[tiab] OR healthy year equivalent*[tiab] OR healthy years equivalent*[tiab] OR pqol[tiab] OR qls[tiab] OR quality of well being[tiab] OR index of wellbeing[tiab] OR qwb[tiab] OR nottingham health profile*[tiab] OR sickness impact profile[tiab] OR health status indicators[mh] OR health utilit*[tiab] OR health status[tiab] OR disutilit*[tiab] OR rosser[tiab] OR willingness to pay[tiab] OR standard gamble*[tiab] OR time trade off[tiab] OR time tradeoff[tiab] OR tto[tiab] OR hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] OR eq[tiab] OR euroqol[tiab] OR euro qol[tiab] OR eq5d[tiab] OR eq 5d[tiab] OR euroqual[tiab] OR euro qual[tiab] OR duke health profile[tiab] OR functional status

questionnaire[tiab] OR dartmouth coop functional health assessment*[tiab] OR (utilit*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR score*[tiab] OR weight[tiab])) OR (preference*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR score*[tiab] OR instrument[tiab] OR instruments[tiab]))))

D.6 POTENTIAL SEARCH TERMS: TOR 6

(< >) Strings to be placed inside (< >) include infantile onset or juvenile late onset or adult late onset or left blank.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase")

AND

("Adherence, Medication" OR "Medication Nonadherence" OR "Nonadherence, Medication" OR "Medication Noncompliance" OR "Noncompliance, Medication" OR "Medication Non-Adherence" OR "Medication Non Adherence" OR "Non-Adherence, Medication" OR "Medication Persistence" OR "Persistence, Medication" OR "Medication Compliance" OR "Compliance, Medication" OR "Medication Non-Compliance" OR "Medication Non Compliance" OR "Non-Compliance, Medication")

AND utilisation OR utilization

AND

(alglucosidase alfa OR myozyme)

D.7 POTENTIAL SEARCH TERMS: TOR 7

(< >) Strings to be placed inside (< >) include infantile onset or juvenile late onset or adult late onset or left blank.

(< >) AND ("Pompe disease" OR "glycogen storage disease II" OR "glycogen storage disease 2" OR "GSD2" OR "GSD II" OR "acid alpha-glucosidase deficiency" OR "GAA deficiency" OR glycogenosis, generalized, cardiac form" OR "cardiomegalia glycogenica diffusa" OR "acid maltase deficiency" OR "AMD" OR "alpha-1,4-glucosidase deficiency" OR "acid maltase") AND ((orphan AND (drug OR therap* OR medicine OR device*)) OR (diagnos* OR (screen OR screening) OR (device* OR test)) OR (future OR novel OR emerging))

APPENDIX E: HORIZON SCAN DATA SOURCES AND EMERGING TECHNOLOGY ASSESSMENT

For the purposes of the horizon scan, the data sources listed in Table E-1 will be searched for emerging technologies for Pompe disease.

Table E-1: List of resources to be used in the horizon scan

Data source	Website
Peer-reviewed databases	
Embase	http://www.ovid.com/site/catalog/databases/903.jsp
PubMed	https://www.ncbi.nlm.nih.gov/pubmed/
Cochrane Library	https://www.cochranelibrary.com/
International organisations	
National Institutes of Health (NIH)	https://www.nih.gov/
NIH National Centre for Advancing Translational Sciences	https://ncats.nih.gov/index.php
NIH Office of Intermural Research Office of Technology Transfer	https://www.ott.nih.gov/resources
NIH National Human Genome Research Institute	https://www.genome.gov/
Early assessment & alert systems	
National Horizon Scanning Centre	https://www.nihr.ac.uk/research-and-impact/emerging-health-technologies/horizon-scanning-research.htm
EuroScan	http://euroscan.org.uk/
SPS NIH	https://www.sps.nhs.uk/?s&cat%5B0%5D=3342
HTA / Independent research organisations	
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
Canadian Agency for Drugs and Technologies in Health (CADTH):	https://www.cadth.ca/
CADTH Health Technology Update	https://www.cadth.ca/reports?keywords=&product_type%5B%5D=107327&sort=field_date%3Avalue-desc&amount_per_page=10&email_address=&page=1
CADTH Issues in Emerging Technology	https://www.cadth.ca/reports?keywords=&result_type[]=report&product_type[]=107322&sort=field_date%3Avalue-desc&amount_per_page=10&email=&page=1
Haute Autorité de Santé (HAS)	https://www.has-sante.fr/portail/jcms/r_1455081/Home-page
National Institute for Health & Clinical Excellence (NICE)	http://www.evidence.nhs.uk/about-evidence-services/content-and-sources/medicines-information
National Coordinating Centre for Health Technology Assessment	http://www.nchta.org
Scottish Medicines Consortium (SMC)	https://www.scottishmedicines.org.uk/about-us/horizon-scanning/
Regulatory agencies	
Therapeutic Goods Administration (TGA)	http://www.tga.gov.au/
US Food and Drug Administration (FDA)	http://www.fda.gov/default.htm
FDA Office of Orphan Drugs Development	https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/officeofscienceandhealthcoordination/ucm2018190.htm
European Medicines Agency (EMA)	http://www.ema.europa.eu/en/
News	
PharmaTimes	http://www.pharmatimes.com/
Healio	http://www.healio.com/
EurekAlert!	http://www.eurekalert.org/
Medpage Today	http://www.medpagetoday.com/
PharmaLive	https://www.pharmalive.com/
PR Newswire	https://www.prnewswire.com/

Data source	Website
Clinical trials registries	
Australian New Zealand Clinical Trials Registry (ANZCTR)	http://www.anzctr.org.au/
EU Clinical Trials Register	https://www.clinicaltrialsregister.eu/
National Institute of Health - U.S. National Library of Medicine	https://clinicaltrials.gov/ct2/home
Current Controlled Trials metaRegister (US and UK clinical trial registers)	http://www.isrctn.com/
Other	
Orphanet	https://www.orpha.net/consor/cgi-bin/index.php
Rare Voices	https://www.rarevoices.org.au/
NORD	https://rarediseases.org/
Eurordis	https://www.eurordis.org
F1000Poster	https://f1000research.com/

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ASHP, American Society of Health-System Pharmacists; CADTH, Canadian Agency for Drugs and Technologies in Health; EMA, European medicines agency; EU, European union; FDA, Food and drug administration; HAS, Haute Autorité de Santé; HTA Health technology assessment; KCE, Belgian Health Care Knowledge Centre; NCCHTA, National Coordinating Centre for Health Technology Assessment; NECA, National Evidence-based healthcare Collaborating Agency; NHS CRD, University of York NHS Centre for Reviews and Dissemination; NHS HTA, National Health Service Health Technology Assessment (UK); NHMRC, National Health and Medical Research Council; NICE, National Institute for Health and Care Excellence; SPS NHS, Specialist Pharmacist Service NHS; SMC, Scottish Medicines Consortium; TGA, Therapeutic goods administration

The developing technology summary sheet in Table E-2 is to be completed for upcoming treatments and tests that could impact future access for Pompe disease patients. The goal of the summary sheet is to provide a synopsis of the identified technology, in addition to its clinical and regulatory progress to date. Furthermore, the table will also provide information regarding other pieces of information that address one or more of the multiple dot points under Section 8.9. Sources for all pieces of information use in the developing technology summary sheet will also be provided for easy referencing.

Table E-2: Developing technology summary sheet

Developing technology summary sheet				
Product brief				
Proprietary name:				
Type of technology (test/treatment [functional agent name]):				
Method of action:				
Stage of development (Pre-clinical – Phase IV):				
Indicated for Pompe disease?				
<ul style="list-style-type: none"> If yes, what is the official indication? 				
Approved for Pompe disease in Australia?				
<ul style="list-style-type: none"> Provide the ARTG number (if available): 				
Registered elsewhere (if yes, list all countries)?				
Clinical trials				
Study title Trial number	Trial status	Intervention/treatment	Site Locations (n)	Trial outcomes (primary and secondary)
Other				
Sources				