Australian Government Department of Health

Review of the Life Saving Drugs Program medicines: Paroxysmal Nocturnal Hemoglobinuria (PNH)

Final Review Protocol

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1 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 (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 paroxysmal nocturnal haemoglobinuria (PNH) medicine was prepared by HealthConsult. Its development was informed by consultations (e.g. with the EP, PNH clinicians) as well as a stakeholder forum (including representatives from the PNH Support Association of Australia; 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 PNH disease medicine.

1.3 TERMS OF REFERENCE

The draft ToR for the Review of LSDP medicine for PNH were open to public consultation from 25th February 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 medicine for PNH are:

- **ToR 1:** Review the prevalence of Paroxysmal Nocturnal Haemoglobinuria (PNH) in Australia.
- **ToR 2:** Review evidence for the management of PNH 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 eculizumab for the treatment of PNH, including 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 PNH.
- **ToR 5:** Assess the value for money of eculizumab under the current funding arrangements by evaluating the benefit of the drug's treatment outcomes and cost.
- **ToR 6:** Review the utilisation of eculizumab 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.

2
ToR 1: Prevalence

This Chapter outlines the methodology to address ToR 1 *"Review the prevalence of Paroxysmal Nocturnal Haemoglobinuria (PNH) in Australia."*

The purpose of ToR 1 is to understand the prevalence of PNH 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 PNH in Australia will need to be undertaken. *Prevalence* refers to the "number or proportion of cases, instances, etc. present in a population at a given time".[1] 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	PNH registry data	Stakeholder consultation[a]
1. What is the prevalence of PNH in Australia?	+	+	+	+
2. What proportion of patients with PNH are eligible to access treatment under the LSDP?	–	+	+	+
3. What proportion of eligible PNH patients are accessing the LSDP?	–	+	+	+
4. Has the prevalence of PNH in Australia changed since government subsidies on drugs for treating PNH became available?	+	+	+	+
If outcomes of ToR2 indicate a change in eligibility criteria				
5. What proportion of PNH patients would be eligible for the LSDP if eligibility criteria is modified?	–	+	+	+

Abbreviations: LSDP, life saving drugs program; PNH, Paroxysmal Nocturnal Haemoglobinuria; 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 PNH. 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 PNH and an appropriate filter to identify reports relating to the incidence and prevalence of PNH will guide the search. Details of the terms to be used are provided in Appendix D.
Databases	• EMBASE • Medline • Cochrane Library
Other means to identify relevant information	• 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	• Full text systematic reviews, literature reviews, clinical trials publications, reports and guidelines reporting on outcome measures for PNH-specific treatment, and data cubes
Search period	• Articles published from 2009[a] • Conference abstracts published since 2017[b]
PICO	• Population: people diagnosed with PNH • 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	• Wrong population: Does not include PNH • Wrong outcome: Does not investigate prevalence of PNH

Abbreviations: ABS, Australian Bureau of Statistics; AIHW, Australian Institute of Health and Welfare; EMA, European Medicines Agency; EMBASE, Excerpta Medica database; MHRA, Medicines & Healthcare products Regulatory Agency; ONS, Office for National Statistics; PBS, Pharmaceutical Benefits Scheme; PNH, Paroxysmal Nocturnal Haemoglobinuria; 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 PNH. However, not all eligible patients may be receiving treatment with the LSDP subsidised PNH medicine (refer to 2.7 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 PNH from when the program commenced data collection on patient applications/re-applications.

It is noted that Australian PNH 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 PNH in Australia. The LSDP patient-level data should provide a solid basis for informing the prevalence of PNH patients who are receiving subsidised therapy within Australia.

2.4 PNH REGISTRY DATA

HealthConsult will seek to access PNH registry data. There is one sponsor-supported registry database of relevance:

- **The Paroxysmal Nocturnal Haemoglobinuria (PNH) Registry**: a rare disease registry sponsored by Alexion.[2] It is a prospective, international, non-interventional study that compiles important data on the natural history and management of patients diagnosed or with signs of PNH. The PNH registry is currently being implemented in 36 locations, including Australia.[3]

The number of Australian patients in the registries will be factored into determining the present PNH prevalence.

2.5 STAKEHOLDER CONSULTATION

Expert opinion will be used to supplement information retrieved through other ToR 1 data sources described above. Expert opinion, will be sought from clinicians and the peak consumer organisation, PNH Support Association of Australia (PNHSAA), to inform factors affecting disease prevalence in Australia; to determine the number of PNH patients being treated within and outside the LSDP; the reasons why individuals are not accessing LSDP drugs; if any PNH 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.[4] 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.

2.6 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 eculizumab under the LSDP
- proportion of eligible patients who are treated under the LSDP
- prevalence of asymptomatic individuals with a confirmed diagnosis, for instance, individuals with PNH clone size ≥ 10% by flow cytometry, but without disease-related events
- prevalence of adults (aged 18 and over) versus paediatric 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, LSDP patient-level data, LSDP dispensing data and the PNH registry.

The systematic review will provide an evidence base of secondary sources indicating the prevalence of PNH 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 PNH cases over time and may therefore need to be factored into calculations to determine total disease prevalence.

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 ToR 1 research question 2. The eligible population will be determined via: 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 PNH cases, pre and post introduction of the LSDP subsidised medicines, 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 eculizumab is available on the LSDP and, also, the population for whom eculizumab should be available, if findings from ToR 2 indicate that a change to current eligibility criteria might be warranted.

2.7 LIMITATIONS

Not all Australian PNH patients will be included 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 trial 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 the commercial registry which are used for clinical trials. Without this trial data, total Australian disease prevalence calculations will likely represent an underestimate.

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

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. The diagnosis of PNH is also not restricted to pathological testing methodologies and therefore there is no relevant National Reference Laboratories (NRL) from which incidence data (to inform the prevalence calculations) could be obtained from.

3 ToR 2: Management of PNH in comparison to LSDP guidelines

This Chapter outlines the methodology to address ToR 2 *"Review evidence for the management of PNH 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 PNH (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 PNH, 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 PNH 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. 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 eculizumab under the LSDP compare with international clinical guidelines. 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 PNH? What is the quality of evidence underpinning this approach?	+	-	+
2. What are the eligibility criteria for initial and ongoing access to LSDP medicines?[a] What is the quality of evidence underpinning these requirements?	+	+	+
3. Are there any inconsistencies between clinical best practice and the LSDP eligibility criteria? If yes, which is more appropriate based on evidence?	+	+	+

Abbreviations: LSDP, life saving drugs program; PNH, Paroxysmal Nocturnal Haemoglobinuria; ToR, term of reference
a Includes investigating reapplication or continuation criteria for those that have responded to therapy and deteriorated (i.e., clone size < 10%)

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 PNH 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 PNH populations (classic PNH, subclinical PNH and PNH with other bone marrow disorder).

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	Synonyms for PNH and an appropriate filter to identify clinical guidelines will guide the search. Details of the terms are provided in Section D.2 of Appendix D.
Databases	Peer reviewed articles • EMBASE • Medline • Cochrane Library Clinical guidelines • Guideline Central (www.guidelinecentral.com) • Australian Clinical Practice Guidelines Portal (www.clinicalguidelines.gov.au) • G-I-N (www.g-i-n.net) • NORD (ww.rarediseases.org) • AHRQ (www.ahrq.gov) • SIGN (www.sign.ac.uk) • NICE (www.nice.org.uk)
Other means to identify relevant information	• PBAC PSDs for PNH medicines • Product information documents for PNH medicines on the ARTG • Other relevant websites (e.g. Rare Voices Australia, PNH Support Association of Australia)
Publication types	• Australian and international evidence-based clinical practice guidelines on the pharmacological management of PNH
Search period	• Articles published from 2012[a] • Conference abstracts published since 2017[b]
Exclusions	• Guidance does not relate to PNH

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; ARTG, Australian Register of Therapeutic Goods; 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; PNH, Paroxysmal Nocturnal Haemoglobinuria; 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 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 PNH 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.[5] 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 the PNHSAA, will be approached to provide comments and insight into:

- the current access criteria
- the role of the required tests in making clinical decisions and in-patient monitoring
- the ongoing access criteria for patients
- the impact of LSDP requirements on a clinician's service.

Any conflicting opinions arising through the consultation process will be managed as per the guidance provided in the PBAC guidelines.[5] 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 PNH and assessing their suitability for eculizumab. The review will outline the current LSDP eligibility criteria for patients to obtain access to eculizumab. 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 (i.e. classic PNH, subclinical PNH and PNH with other bone marrow disorder). 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 qualitative data gathered through stakeholder consultations together, with secondary data sources, will provide the evidence base to answer research questions 1, 2 and 3 of ToR 2.

3.6 LIMITATIONS

There is the possibility that there are (a) no formal clinical guidelines for the treatment of PNH, 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 PNH 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.

4 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 eculizumab for the treatment of PNH, including 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 the current LSDP PNH medicine (i.e. eculizumab) for the treatment of PNH and compare this to the natural history of the disease in the absence of such treatments and to the initial expectations at the time of listing on the LSDP.

4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3

To address ToR 3, the current LSDP subsidised medicine, eculizumab 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 the PNH 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 eculizumab compare to when it was listed on the LSDP?[a, b]	+	+	+
Life extension			
2. Is there evidence that eculizumab has stabilised disease progression and/or extended survival?[a, b]	+	+	+
3. Are the age-adjusted rates of mortality different between eculizumab treated patients and natural disease history? [a, b]	+	+	+
If outcomes of ToR2 indicate a change in eligibility criteria			
4. What is the effectiveness and safety of eculizumab alternate populations?[c]	+	+	+

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

The primary population of interest, patients with PNH, is defined by the current LSDP eligibility guidelines, which require confirmation of the diagnosis of PNH by:

- demonstration of PNH granulocyte clone size equal to or greater than 10% by flow cytometry
- a raised lactate dehydrogenase (LDH) level.

Additionally, to receive treatment with eculizumab under the LSDP, patients must satisfy at least one of[6]:

- *Thrombosis:* This is a thrombotic or embolic event which required the institution of therapeutic anticoagulant therapy.
- *Transfusions:* Evidence that the patient has been transfused with at least four units of red blood cells in the last twelve months.
- *Anaemia:* Chronic or recurrent anaemia where causes other than haemolysis have been excluded and demonstrated by more than one measure of less than or equal to 70g/L or by more than one measure of less than or equal to 100 g/L with concurrent symptoms of anaemia.
- *Pulmonary insufficiency:* Debilitating shortness of breath and/or chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded.
- Renal insufficiency: History of renal insufficiency, demonstrated by an eGFR less than or equal to 60mL/min/1.73m2, where causes other than PNH have been excluded.
- *Smooth muscle spasm:* Recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded.

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 eculizumab to placebo to identify head to head studies[a]
Population	Australian PNH patients who are eligible to receive LSDP funded medicines
Intervention	Eculizumab (Soliris)
Comparator	Supportive care (or placebo in initial RCT)
Outcomes	• 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 eculizumab was reimbursed under the LSDP) will be reported: ➢ incidence of and time to occurrence of key clinical events including: ▪ thrombosis ▪ intravascular haemolysis ▪ transfusions, including transfusion dependence ▪ anaemia ▪ pulmonary insufficiency (SOB, New York Heart Association Class III, pulmonary arterial ▪ hypertension) ▪ renal insufficiency (eGFR less than or equal to 60mL/min/1.73m^2) ▪ smooth muscle spasm (severe pain requiring hospitalisation and/or narcotic analgesia) ➢ fatigue ➢ quality of life ➢ overall survival ➢ safety and adverse events related to eculizumab treatment (including serious infections and meningococcal antibiotic prophylaxis as an alternative for patients unable or unwilling to be vaccinated) • In addition, outcomes for other endpoints that may be of interest given the findings from ToR 2 will be presented (to the extent that they are available)
Other SLR considerations	• 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 (stratified by paediatric and adult)

Abbreviations: GFR, Glomerular filtration rate; LSDP, Life Saving Drugs Program; PNH, Paroxysmal Nocturnal Haemoglobinuria; RCT, randomized controlled trial; SOB, shortness of breath; SLR; systematic literature review; 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]	• Synonyms for PNH and an appropriate filter to identify articles on clinical effectiveness and safety will guide the search. Details of the terms are provided in Section D.3 of Appendix D.
Databases of peer-review literature	• 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	• 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 eculizumab; Product information documents for PNH medicines on the ARTG; AIHW National Death Index data and Cause of Death data; Alexion website, PNH published registry data reports)
Publication types	• Studies in humans • Studies published in English and articles not published in English • Exclude: editorials, letters, non-clinical studies
Search period	• Evidence from the initial LSDP listing trials will be included[i] • Articles published from 2012[j] • Conference abstracts published since 2017[k]
Study exclusion criteria[b]	• Duplicate data • Wrong study type: Not a randomised controlled trial • Wrong population: Does not include patients with PNH • Wrong intervention: Incorrect intervention (not eculizumab) • Wrong comparator: Not compared to the relevant comparator (placebo, or standard therapy in absence of placebo)

Abbreviations PNH, Paroxysmal Nocturnal Haemoglobinuria; AIHW, Australian Institute of Health and Welfare; ARTG, Australian Register of Therapeutic Goods; LSDP, Life Saving Drugs Program; MeSH, medical subject headings; PBAC, Pharmaceutical Benefits Advisory Committee; PNH, Paroxysmal Nocturnal Haemoglobinuria; 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 eculizumab 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 medicine in the trial setting with effectiveness and safety of the medicine 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 B.4). 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 included on the LSDP 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 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 subsided 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 PNH. 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 dataset will be undertaken to assess the impact of eculizumab 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 thromboembolic (i.e., haemolysis, anaemia), transfusion, and fatigue 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, alternative treatment regimens and again compared to original pivotal trial results. The limitations to this analysis are discussed in Section 4.6.

To inform research question 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 PNH 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 different PNH 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 etc. Additional analysis will be presented comparing consistencies in dosing of eculizumab 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 the sponsor). 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). To the extent that it is possible, differences in thrombosis, intravascular haemolysis, fatigue, transfusions, and anaemia will be assessed.

LSDP dispensing data will be also 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 and between different treatments, 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 the doses currently being used to the dosing used in the original trials to the recommended dose in the TGA approved PI.

Research questions 2 and 3 will be informed by the systematic literature review on the natural history of PNH 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 interventions 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 eculizumab is available on the LSDP and, also, the population for who eculizumab 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 only collected on symptomatic patients who qualify for LSDP funded medicines. There is no asymptomatic or 'control group' of patients that have PNH and who do not qualify for LSDP funded medicines. The PNH 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 PNH 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.

5 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 PNH."*

The purpose of ToR 4 is to identify the treatment outcomes that are highly valued by patients with PNH 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".[7] 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 PNH, and their clinicians, who are being treated with the LSDP medicine for PNH?	+	+	+
2. How can administration of the LSDP be improved to help patients with PNH and their clinicians?	–	–	+

Abbreviations: LSDP, life saving drugs program; PNH, Paroxysmal Nocturnal Haemoglobinuria; 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 PNH PROs related to eculizumab. 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 PNH and an appropriate filter to identify reports relating to patient-reported outcomes in PNH 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	• EMBASE • Medline • Cochrane Library
Other means to identify evidence	• Clinical trial articles included for analysis in ToR 3 • Clinician input and Clinician international sponsor registry data (The PNH Registry) • Scan for relevant grey literature, including reports from PNH 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: ➢ 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	• Full text reviews, clinical trials, reports and guidelines reporting on patient-centred outcome measures for the treatment of PNH. • English language and reputable trials not published in English (translated by an external provider)
Search period	• Articles published from 2012[b] • Conference abstracts published since 2017[c]
Study exclusion criteria	• Does not relate to patients with PNH. • 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; PNH, Paroxysmal Nocturnal
Haemoglobinuria; PRO, patient reported outcome; ToR, Term of Reference.
a Social media websites include PNH Registry
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 eculizumab. 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. PNHSAA), (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.[4]

The stakeholder consultation process will be designed to gather data to address the 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: age, gender, subtype of disease, 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[8, 9] (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 the PNH medicine funded under the LSDP.

Being a rare disease, PNH patient populations are inherently small. As such, PROM tools to measure PNH-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

6 ToR 5: Value for money of LSDP PNH medicines

This Chapter outlines the methodology to address ToR 5 *"Assess the value for money of eculizumab 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 PNH 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 PNH patient with the LSDP medicine? 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 with PNH? 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 with PNH? Is this different to what was expected at the time the medicine was included on the LSDP (e.g. actual vs predicted)?	+	+	–	–	+	–	–
4. How do the costs and outcomes associated with eculizumab 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; PNH, Paroxysmal Nocturnal Haemoglobinuria; ToR, term of reference
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.[10] 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	• Synonyms for PNH 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	• 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	• Websites of HTA and reimbursement agencies: NICE, CADTH, SMC • Manual scan of reference lists of included articles
Publication types	• Full text systematic reviews, literature reviews, clinical trial publications, economic evaluation reports, and reimbursement application reports • Available in English
Search period	• Articles published from 2012[a] • Conference abstracts published since 2017[b]
Study exclusion criteria	• Does not relate to patients with PNH • 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; HEED, Health Economic Evaluations Database; HTA, Health Technology Assessment; NICE, National Institute for Health and Care Excellence; PNH, Paroxysmal Nocturnal Haemoglobinuria; 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 PNH. 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 PNH.

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 PNH 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 PNH. 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 PNH. 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 PNH. The use of medicines unrelated to PNH 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 PNH will be excluded from the modelled economic evaluation. The list of concomitant medicines for each PNH 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 PNH 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 PNH will be sourced in accordance with guidance contained in the Manual of resource items and their associated unit costs.[11] 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.[5] Expert opinion may include data obtained through surveys that collect clinician time, and/or international 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 guidelines[5], 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 PNH.

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 eculizumab and for standard of care will be reported. Standard of care will be clearly defined. This may include non-specific standard of care therapies. A pair-wise comparison 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.[5] 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 PNH (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 PNH, 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 discussions with the LSDP EP.

7 ToR 6: Utilisation of LSDP PNH medicines

This Chapter outlines the methodology to address ToR 6 *"Review the utilisation of eculizumab 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 the LSDP subsidised PNH medicine, 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 year and in total) have been treated under the LSDP? How does this compare with expectations at the time eculizumab was included on the LSDP?	-	+	+	-	+	-
2. How many units (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 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 eculizumab 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?	-	+	+	-	-	+
8. What is the average dose (and distribution around average dose)? How does this compare to the approved[b] use of the medicine?	+	+	+	-	+	+
9. What is the average interval between doses (and distribution around this	+	+	+	-	-	+

ToR 6 research questions	Data sources					
	Systematic literature review[a]	LSDP patient-level data	LSDP dispensing data	LSDP pricing data	PBAC submissions	Stakeholder consultation
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
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 the LSDP subsidised PNH 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	• Synonyms for PNH 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	• EMBASE • Medline • Cochrane library
Other means to identify relevant information	• PBAC PSDs • Manual scan of reference lists of included articles • Medicine Product Information (TGA) • LSDP documents (Australian Government Department of Health)
Publication types	• Full text systematic reviews, literature reviews, clinical trial publications, and reimbursement application reports • Available in English
Search period	• Articles published from 2009[a] • Conference abstracts published since 2017[b]
Study exclusion criteria	• Does not relate to patients with PNH

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 PNH 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 PNH 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. 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 5, 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 submissions. 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 eculizumab 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 eculizumab will be based on the exclusion criteria from the PNH guidelines.[6] 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 if 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.

8 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 PNH 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 eculizumab 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 PNH Support Association of Australia

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 PNH 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	• Synonyms for PNH and an appropriate filter to identify clinical guidelines will guide the search. Details of the terms are provided in Appendix D.
Limits	• English and reputable trials not published in English AND humans
Search period	• Articles published from 2015[a] • Conference abstracts published since 2017[b]

Abbreviations: PNH, Paroxysmal Nocturnal Haemoglobinuria
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 PNH 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 PNH 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 PNH 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 PNH patients but may not necessarily go through the traditional regulatory and HTA route can also be identified. The potential impact of new innovations on PNH 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 PNH 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 (e.g. chaperone/gene/substrate reduction therapy).

8.8 OTHER

Other resources, as described in Appendix E, will also be investigated. This is not only to 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 to PNH treatments.

Also, stakeholders consulted as part of the other ToR, 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 PNH?
- 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.

9 References

1. Australian Government. Department of Health Acronyms and Glossary. http://www.health.gov.au/internet/main/publishing.nsf/content/glossary.
2. ClinicalTrials.gov, Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry. **2018**.
3. PNHRegistry.com, **2019**.
4. Australian Governemt. The Pharmaceutical Benefits Advisory Committee (PBAC), Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee. 2016.
5. Australian Government. Department of Health, Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee. Version 5.0. 2016.
6. Australian Government. Department of Health., Life Saving Drugs Program (LSDP) guidelines for initial application and annual reapplication for subsidised treatment for Paroxysmal Nocturnal Haemoglobinuria (PNH). **2018**.
7. Australian Commission on Safety and Quality in Health Care Patient-Reported Outcome Measures. https://www.safetyandquality.gov.au/our-work/indicators/patient-reported-outcome-measures/.
8. Rothrock, N. E.; Kaiser, K. A.; Cella, D., Developing a valid patient-reported outcome measure. *Clin Pharmacol Ther* **2011,** *90* (5), 737-42.
9. Deshpande, P. R.; Rajan, S.; Sudeepthi, B. L.; Abdul Nazir, C. P., Patient-reported outcomes: A new era in clinical research. *Perspect Clin Res* **2011,** *2* (4), 137-44.
10. Canadian Agency for Drugs and Technologies in Health (CADTH) Strings Attached: CADTH's Database Search Filters. https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#guide (accessed 21 January 2019).
11. Australian Government. Department of Health, Manual of resource items and their associated unit costs. Version 5.0. 2016.
12. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D. G.; Group, P., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* **2009,** *151* (4), 264-9, W64.
13. Coleman, K.; Norris, S.; Weston, A.; Grimmer-Somers, K.; Hillier, S.; Merlin, T.; Tooher, R. J. C. N., NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. **2005**.
14. Shea, B. J.; Reeves, B. C.; Wells, G.; Thuku, M.; Hamel, C.; Moran, J.; Moher, D.; Tugwell, P.; Welch, V.; 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.
15. Guyatt, G.; Oxman, A. D.; Akl, E. A.; Kunz, R.; Vist, G.; Brozek, J.; Norris, S.; Falck-Ytter, Y.; Glasziou, P.; Jaeschke, R. J. J. o. c. e., GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. **2011,** *64* (4), 383-394.
16. Balshem, H.; Helfand, M.; Schünemann, H. J.; Oxman, A. D.; Kunz, R.; Brozek, J.; Vist, G. E.; Falck-Ytter, Y.; Meerpohl, J.; Norris, S. J. J. o. c. e., GRADE guidelines: 3. Rating the quality of evidence. **2011,** *64* (4), 401-406.
17. Consortium, A. N. S. The AGREE II Instrument [Electronic version]. https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf (accessed 24 January 2019).
18. Higgins, J.; Sterne, J.; Savović, J.; Page, M.; 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*.
19. Borowitz, M. J.; Craig, F. E.; DiGiuseppe, J. A.; Illingworth, A. J.; Rosse, W.; Sutherland, D. R.; Wittwer, C. T.; Richards, S. J., Guidelines for the diagnosis and monitoring of paroxysmal

nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry Part B: Clinical Cytometry* **2010,** *78* (4), 211-230.
20. Hillmen, P.; Lewis, S.; Bessler, M.; Luzzatto, L.; Dacie, J. V., Natural history of paroxysmal nocturnal hemoglobinuria. *New England Journal of Medicine* **1995,** *333* (19), 1253-1258.
21. Brodsky, R. A., How I treat paroxysmal nocturnal hemoglobinuria. *Blood* **2009,** *113* (26), 6522-6527.
22. Sahin, F.; Akay, O. M.; Ayer, M.; Dal, M. S.; Ertop, S.; Ilhan, O.; Karakus, V.; Ozcan, M. A.; Ozkocaman, V.; Ozsan, H., Pesg PNH diagnosis, follow-up and treatment guidelines. *American journal of blood research* **2016,** *6* (2), 19.
23. de Latour, R. P.; Mary, J. Y.; Salanoubat, C.; Terriou, L.; Etienne, G.; Mohty, M.; Roth, S.; de Guibert, S.; Maury, S.; Cahn, J. Y., Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood* **2008,** *112* (8), 3099-3106.
24. Australian Government., Australian product information - Soliris® (Eculizumab *RMC*) concentrated solution for intravenous infusion. 2018.

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 PNH.

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 PNH 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 PNH 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 PNH, 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 PNH, that might compromise the effectiveness of the drug treatment; and

(4) be an Australian citizen or permanent Australian resident who qualifies for Medicare.[6]

LSDP patient-level data collected annually for patients on the LSDP receiving PNH treatment with eculizumab is presented in Table A-1.

Table A-1: LSDP data collected annually from PNH patients

Patient Level Program Data
Laboratory tests
Hb ($x10^9$/L)
Platelets ($x10^9$/L)
WCC ($x10^9$/L)
Reticulocytes ($x10^9$/L)
Neutrophils ($x10^9$/L)
Granulocyte clone size (%)
Lactate Dehydrogenase and upper limit of normal for the reporting laboratory (ULN)
Multiple of ULN
Urea and electrolytes
eGFR
Iron studies
Specific indication for funding (as applicable)
Thrombosis
Transfusions
Anaemia
Pulmonary insufficiency
Renal insufficiency

Patient Level Program Data
Smooth muscle spasm
Other
Transfusion history (date of transfusions & number of units)
Quality of life (Narrative including fatigue)
PNH related medications
Compliance
Anecdotal information from treating physician
Other conditions/diagnosis
Vaccination date

Source: Australian Government Department of Health. Accessed 2019. Life Saving Drugs Program (LSDP) guidelines for initial and annual reapplication for subsidised treatment for Paroxysmal Nocturnal Haemoglobinuria (PNH).
Abbreviations: Hb, haemoglobin; WCC, white cell count; ULN, upper limit of normal; eGFR, estimated Glomerular filtration rate; PNH, paroxysmal nocturnal haemoglobinuria

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 the dispensing records for patients on the LSDP receiving PNH treatment with eculizumab is presented in Table A-2.

Table A-2: LSDP dispensing data collected from PNH 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 (5mg vial)
Dispensed amount (35mg 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) dispensing records.

A.3 LSDP PRICING DATA

The LSDP pricing data includes details on the arrangement between the Department and the pharmaceutical company that owns the medication for PNH. The data collected regarding the pricing of LSDP medications is presented in Table A-3.

Table A-3: LSDP pricing data for PNH medications

LSDP Pricing Data
General information
Medicine
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)
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 PNH -overview and pricing

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
- estimated number of patients that will take the medicine

A.5 RARE DISEASE REGISTRIES

Rare disease registries are typically run by international pharmaceutical companies, such as Alexion. 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 database of particular interest for the current Review is:

- Paroxysmal Nocturnal Haemoglobinuria (PNH) Registry. https://www.pnhregistry.com/

A.6 PNH SUPPORT ASSOCIATION AUSTRALIA

The PNH Support Association of Australia (PNHSAA) is a charitable non-profit organisation whose mission is to support Australians diagnosed with PNH and their families and friends, to increase awareness and

understanding of PNH and advocate best possible care for PNH patients. The objectives of the PNHSAA are to:

- facilitate communication between Members and provide a strong support base to empower PNH patients to manage their condition positively
- provide information about treatment options, current research, PNH specialists and related topics to Members and the Australian community
- establish and maintain a portal through which to direct Members to other available means of practical support and PNH-related information, including participating in related domestic and international support group networks
- provide advocacy services to Members to raise public awareness of PNH and ensure patients have access to the best possible treatment and care
- undertake, facilitate and fund research in PNH and associated diseases
- increase awareness of PNH and associated diseases within the medical profession and the wider community.

PNHSAA 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.[12] 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 eculizumab for the treatment of PNH. 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. thrombosis, intravascular haemolysis, anaemia, and fatigue outcomes). 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 B.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.[12]

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).[13] Systematic reviews will be critically appraised using the AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) checklist (Appendix B.3). [14] 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. [15] The GRADE system classifies the overall quality/level of the body of evidence for each outcome into one of four scores: [16]

(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. [15]

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: • 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: • 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) checklist[17] 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.	☐ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☐ Target(s) (e.g., patient population, society)	
2. QUESTIONS Report the health question(s) covered by the guideline, particularly for the key recommendations.	☐ Target population ☐ Intervention(s) or exposure(s) ☐ Comparisons (if appropriate) ☐ Outcome(s) ☐ Health care setting or context	
3. POPULATION Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.	☐ Target population, sex and age ☐ Clinical condition (if relevant) ☐ Severity/stage of disease (if relevant) ☐ Comorbidities (if relevant) ☐ 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.	☐ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☐ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☐ 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.	☐ 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) ☐ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☐ 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.	☐ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☐ 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.	☐ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☐ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☐ Search terms used (e.g., text words, indexing terms, subheadings) ☐ Full search strategy included (e.g., possibly located in appendix)	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE #
8. EVIDENCE SELECTION CRITERIA Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.	☐ Target population (patient, public, etc.) characteristics ☐ Study design ☐ Comparisons (if relevant) ☐ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	
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.	☐ Study design(s) included in body of evidence ☐ Study methodology limitations (sampling, ☐ blinding, allocation concealment, analytical ☐ methods) ☐ Appropriateness/relevance of primary and ☐ secondary outcomes considered ☐ Consistency of results across studies ☐ Direction of results across studies ☐ Magnitude of benefit versus magnitude of harm ☐ 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.	☐ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☐ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☐ 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.	☐ Supporting data and report of benefits ☐ Supporting data and report of harms/side effects/risks ☐ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☐ 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.	☐ How the guideline development group linked and used the evidence to inform recommendations ☐ Link between each recommendation and key evidence (text description and/or reference list) ☐ 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.	☐ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☐ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☐ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☐ 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.	☐ A statement that the guideline will be updated ☐ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	
DOMAIN 4: CLARITY OF PRESENTATION		

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE #
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.	☐ A statement of the recommended action ☐ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☐ Relevant population (e.g., patients, public) ☐ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☐ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. MANAGEMENT OPTIONS Describe the different options for managing the condition or health issue.	☐ Description of management options ☐ Population or clinical situation most appropriate to each option	
17. IDENTIFIABLE KEY RECOMMENDATIONS Present the key recommendations so that they are easy to identify.	☐ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☐ 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.*	☐ Types of facilitators and barriers that were considered ☐ 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) ☐ 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) ☐ 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.*	☐ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals o Solutions linked to barrier analysis (see Item 18) o Tools to capitalize on guideline facilitators (see Item 18) o Outcome of pilot test and lessons learned	
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☐ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☐ 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.) ☐ Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) ☐ 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.*	☐ Criteria to assess guideline implementation or adherence to recommendations ☐ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE #
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY Report the funding body's influence on the content of the guideline.	☐ The name of the funding body or source of funding (or explicit statement of no funding) ☐ 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.	☐ Types of competing interests considered ☐ Methods by which potential competing interests were sought ☐ A description of the competing interests ☐ 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,[14] 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: ☐ Population ☐ Intervention ☐ Comparator group ☐ Outcome	Optional (recommended) ☐ Timeframe for follow-up	☐ Yes ☐ 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?		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: ☐ review question(s) ☐ a search strategy ☐ inclusion/exclusion criteria ☐ a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: ☐ a meta-analysis/synthesis plan, if appropriate, *and* ☐ a plan for investigating causes of heterogeneity ☐ justification for any deviations from the protocol	☐ Yes ☐ Partial Yes ☐ No
3. Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: ☐ *Explanation for* including only RCTs ☐ OR *Explanation for* including only NRSI ☐ OR *Explanation for* including both RCTs and NRSI		☐ Yes ☐ No
4. Did the review authors use a comprehensive literature search strategy?		
For Partial Yes (all the following): ☐ searched at least 2 databases (relevant to research question) ☐ provided key word and/or search strategy ☐ justified publication restrictions (e.g. language)	For Yes, should also have (all the following): ☐ searched the reference lists/bibliographies of included studies ☐ searched trial/study registries ☐ included/consulted content experts in the field ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review	☐ Yes ☐ Partial Yes ☐ No
5. Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer		☐ Yes ☐ No
6. Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ 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		☐ Yes ☐ No
7. Did the review authors provide a list of excluded studies and justify the exclusions?		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
For Partial Yes: ☐ 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: ☐ justified the exclusion from the review of each potentially relevant study	☐ Yes ☐ Partial Yes ☐ No
8. Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): ☐ described population ☐ described interventions ☐ described comparators ☐ described outcomes ☐ described research designs	For Yes, should also have ALL the following: ☐ described population in detail ☐ described interventions in detail (including doses where relevant) ☐ described comparators in detail (including doses where relevant) ☐ described study's setting ☐ timeframe for follow-up	☐ Yes ☐ Partial Yes ☐ No
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: ☐ unconcealed allocation, *and* ☐ 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: ☐ allocation sequence that was not truly random, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
NRSI For Partial Yes, must have assessed RoB: ☐ from confounding, *and* ☐ from selection bias	For Yes, must also have assessed RoB: ☐ methods used to ascertain exposures and outcomes, *and* ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs
10. Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: ☐ 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		☐ Yes ☐ No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		
RCTs For Yes: ☐ the authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present ☐ AND investigated the causes of any heterogeneity		☐ Yes ☐ No ☐ No meta-analysis conducted

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
For NRSI For Yes: ☐ the authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ 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 ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review		☐ Yes ☐ No ☐ 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?		
For Yes: ☐ included only low risk of bias RCTs ☐ 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		☐ Yes ☐ No ☐ 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: ☐ included only low risk of bias RCTs ☐ 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		☐ Yes ☐ 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: ☐ There was no significant heterogeneity in the results ☐ 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		☐ Yes ☐ 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: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias		☐ Yes ☐ No ☐ 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?		

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both		
For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest		☐ Yes ☐ 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)[18] 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 RoB2 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?		Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y / PY / PN / N / 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?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA / Y / PY / PN / N / NI
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI 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 / Y / PY / PN / N / 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?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were important co-interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. Could failures in implementing the intervention have affected the outcome?		Y / PY / PN / N / NI
2.5. Did study participants adhere to the assigned intervention regimen?		Y / PY / PN / N / NI

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

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 / Y / PY / PN / N / 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?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?		NA / Y / PY / PN / N / NI
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / 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?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y / PY / PN / N / NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / PN / N / 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 / Y / PY / PN / N / 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?		Y / PY / PN / N / NI

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

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?		Y / PY / PN / N / NI
5.3 ... multiple analyses of the data?		Y / PY / PN / N / 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

The 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 2.2. If Y/PY to 2.1: Were the post- intervention variables that influenced selection likely to be associated with intervention? 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?	Y / PY / PN / N / NI NA / Y / PY / PN / N / NI 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
	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 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

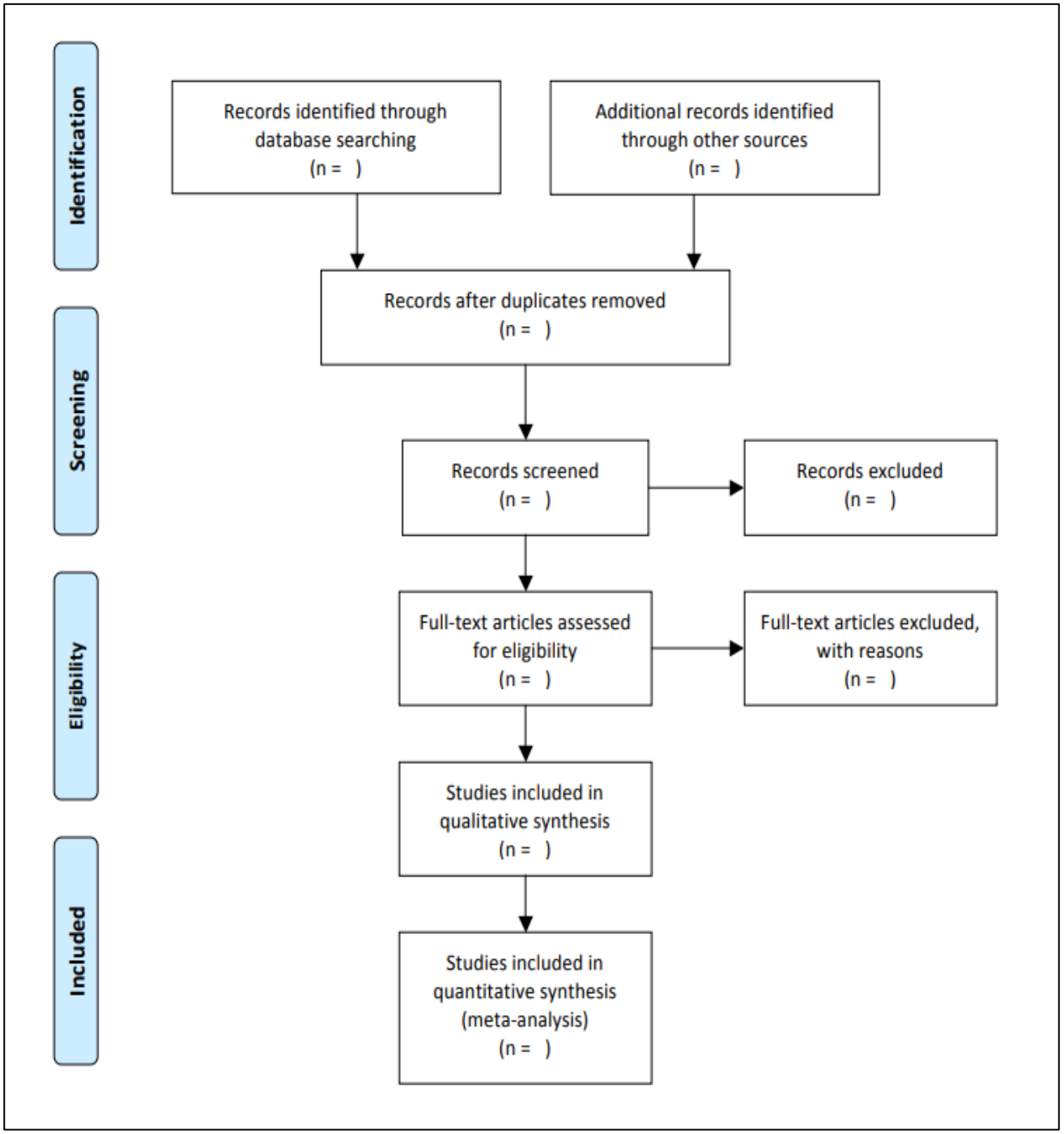
Bias domain	Signalling questions	Response options
	Optional: What is the predicted direction of bias due to missing data?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in measurement of outcomes		
	6.1 Could the outcome measure have been influenced by knowledge 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 *measurements* within the outcome domain?	Y / PY / PN / N / NI
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Y / PY / PN / N / NI
	7.3 ... different *subgroups?*	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: PNH IN AUSTRALIA

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

C.1 DESCRIPTION AND DIAGNOSIS OF PNH

PNH is a hematopoietic stem cell disease which can arise de novo or in the setting of aplastic anaemia and is caused by mutations in the *PIGA* gene. The *PIGA* gene is needed for the biosynthesis of glycophosphatidylinositol (GPI) anchors. Mutations in this gene cause a reduction or absence of glycosyl phosphatidylinositol-anchored proteins (GPI-AP). Two of these proteins, CD55 and CD59, are complementary regulatory proteins and the absence of these proteins render PNH erythrocytes susceptible to haemolysis, causing free haemoglobin to be released into the plasma. This causes the many clinical manifestations of PNH: dysphagia, lethargy, erectile dysfunction, chronic renal failure, pulmonary hypertension, anaemia, haemoglobinuria, thrombophilia, and bone marrow failure.[19, 20]

The disease does not appear to be associated with either ethnicity or gender, but the onset of the disease is typically in the middle of life. One study found the median age at diagnosis was 42 years.[20] PNH is associated with reduction of life expectancy, with one study reporting that the median survival after diagnosis was 10 years, with the majority of deaths directly related to PNH.[20] Thrombosis is the leading cause of death, but other causes in PNH include bone marrow failure, renal failure, myelodysplastic syndrome, and leukaemia.[21]

Flow cytometry to establish the absence or severe deficiency of CD55 or CD59 is the gold standard in the diagnosis of PNH.[22] The diagnosis of PNH is established by at least two different GPI protein deficiencies within two different cell lines from granulocytes, monocytes, or erythrocytes. Currently, the best way to determine leukocyte PNH clones is with fluorescently labelled aerolysin (FLAER) which binds directly to the GPI anchor protein and is therefore absent from GPI-anchor-deficient cells. Patients should be tested for PNH if they present with clinical indicators such as intravascular haemolysis as evidenced by haemoglobinuria or elevated plasma haemoglobin; evidence of haemolysis with accompanying iron deficiency, abdominal pain, thrombosis, granulocytopenia or thrombocytopenia; other acquired Coombs'-negative, non-schistocytic, non-infectious haemolytic anaemia; thrombosis with unusual features such as unusual sites, signs of accompanying haemolytic anaemia, or unexplained cytopenia; or evidence of bone marrow failure.

Three sub-types of PNH exist: classic PNH, sub-clinical PNH, and PNH with another bone marrow disorder such as aplastic anaemia, myelodysplasia etc.

Classic PNH is characterised by a PNH granulocyte clone size of equal to or greater than 10% and a raised LDH level of at least 1.5 times the upper limit of normal. These are patients at significant risk of losing their lives to the disease, with 35% dying within 5 years of diagnosis and 10-year mortality of approximately 50%. Compared to the two other sub-types of PNH, classic PNH patients have the highest risk of thrombosis and the worst survival.[23] Of the three sub-types of PNH, only those with classic PNH are eligible to receive eculizumab under the LSDP.

Sub-clinical PNH is characterised by a PNH granulocyte size of less than 10%. This group represents a less severe form of the disease with no clinical or laboratory evidence of haemolysis. However small numbers of GPI-AP-deficient haematopoietic cells (erythrocytes, granulocytes, or both) are detected by flow cytometry.[22] These patients are ineligible to receive eculizumab under the LSDP as PNH granulocyte size of less than 10% is a specific exclusion criteria (Table C-2) and they should be monitored for progression of their disease.

The final sub-type of PNH presents with another bone marrow disorder such as aplastic anaemia or myelodysplastic syndrome. This type of PNH must be diagnosed by bone marrow analysis in addition to the

investigations to diagnose PNH. These patients experience fewer thrombotic events (27.8% of AA-PNH patients experienced a thrombotic event within a 10-year period compared with 37.9% of patients with classic PNH), but 10-year survival was no different from classic PNH.[23]

A comparison of the characteristics associated with the sub-types of PNH are presented in Table C-1.

Table C-1: Comparison of characteristics associated with different sub-types of PNH

Feature	Classic PNH	Sub-clinical PNH	PNH with bone marrow disorder
Granulocyte clone size	≥10%	<10%	≥10%
Haemolytic activity	Yes	No	Yes
Presentation	Abdominal pain, haemolysis, peripheral blood abnormalities (anaemia, thrombocytopenia, neutropenia), thrombosis, fatigue, haemoglobinuria, smooth muscle dystonias	Peripheral blood abnormalities (anaemia, thrombocytopenia, neutropenia), fatigue	Abdominal pain, haemolysis, peripheral blood abnormalities (anaemia, thrombocytopenia, neutropenia), thrombosis, fatigue, haemoglobinuria, smooth muscle dystonias evidence of bone marrow deficiency (aplastic/hypoplastic anaemia, myelodysplastic syndrome, unexplained cytopenia)
Survival	Least favourable (equal to AA-PNH)	Most favourable	Least favourable (equal to classic PNH)

C.2 ACCESS TO LSDP MEDICINES FOR PATIENTS WITH PNH

The LSDP subsidises the full cost of one medication used to treat patients with PNH. Patients need to satisfy the criteria set out in Table C-2 to be eligible for LSDP subsidies.

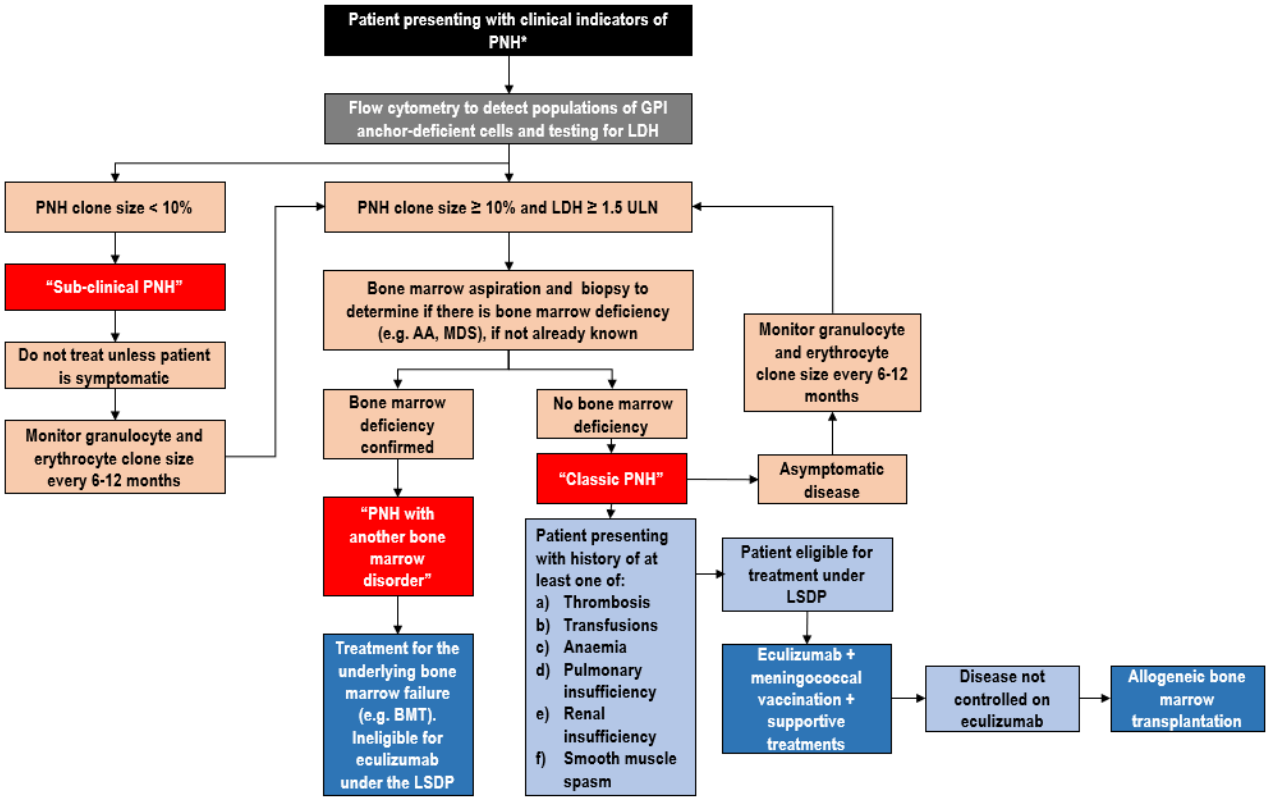
Table C-2: LSDP Guidelines on patient eligibility criteria

Overarching criteria for all patients	Criteria for initial application	Criteria for ongoing treatment	Exclusion criteria
• Patient is permanent Australian resident who qualifies for Medicare. • Patient is not suffering from any other medical condition, including complications or sequelae of the primary condition that might compromise the effectiveness of the 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. • 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.	**(a) Diagnosis of PNH:** the diagnosis must have been established by flow cytometry. The patient must have a PNH granulocyte clone size equal to or greater than 10%. The patient must have a raised lactate dehydrogenase level (value at least 1.5 times the upper limit of normal for the reporting laboratory). **AND** **(b) Vaccination**: as eculizumab increases the risk of meningococcal infections, the patient must receive meningococcal vaccination prior to or at the time of initiating eculizumab. Patients who initiate eculizumab treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Revaccination must occur in accordance with the current version of the Australian Immunisation Handbook. **Plus at least ONE of the points (c) to (h) below** **(c) Thrombosis:** a thrombotic or embolic event which required the institution of therapeutic anticoagulant therapy. **(d) Transfusions:** evidence that the patient has been transfused with at least four units of red blood cells in the last twelve months. **(e) Anaemia:** chronic or recurrent anaemia where causes other than haemolysis have been excluded and demonstrated by more than one measure of less than or equal to 70g/L or by more than one measure of less than or equal to 100 g/L with concurrent symptoms of anaemia. **(f) Pulmonary insufficiency:** debilitating shortness of breath and/or chest pain resulting in limitation of normal activity (New York Heart Association Class III) and/or established diagnosis of pulmonary arterial hypertension, where causes other than PNH have been excluded. **(g) Renal insufficiency:** history of renal insufficiency, demonstrated by an eGFR less than or equal to 60mL/min/1.73m^2, where causes other than PNH have been excluded. **(h) Smooth muscle spasm:** Recurrent episodes of severe pain requiring hospitalisation and/or narcotic analgesia, where causes other than PNH have been excluded.	• The treating physician must submit a separate 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 PNH 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 these guidelines. • The treating physician must also ensure meningococcal vaccination is up-to-date for patients who are receiving subsidised treatment with eculizumab for PNH through the LSDP. Subsidised treatment may continue unless one or more of the following situations apply: • failure to comply adequately with treatment or measures • failure to provide data, copies of the test results and the Excel spreadsheet for PNH, 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.	Patients are not eligible for subsidised treatment with eculizumab for the treatment of PNH through the LSDP if they meet any of the following criteria: • a granulocyte clone size below 10% • Aplastic anaemia with two or more of the following: neutrophil count below 0.5x10^9/L, platelet count below 20x10^9/L, reticulocytes below 25x10^9/L, or severe bone marrow hypocellularity. • Patients with a presence of another life threatening or severe disease where the long-term prognosis is unlikely to be influenced by therapy (for example acute myeloid leukemia or high-risk myelodysplastic syndrome. • The presence of another medical condition that might reasonably be expected to compromise a response to therapy. • Patients participating in an active clinical trial are not eligible for subsidised treatment through the LSDP.

Source: Australian Government. Department of Health (2018) *Life Saving Drugs Program (LSDP) guidelines for initial application and annual reapplication for subsidised treatment for PNH.*[6]

Figure C.1 provides a simplified clinical treatment algorithm of how patients diagnosed with PNH obtain access to treatment on the LSDP. More information on how the current guidelines determine access to PNH medication can be found in Table C-2 of 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.

Figure C.1: Clinical treatment algorithm for PNH patients



Source: Borowitz et al. 2010[19], Sahin et al. 2016[22], Brodsky 2009[21], LSDP Guidelines for application and reapplication - PNH[6]
Abbreviations: PNH, paroxysmal nocturnal haemoglobinuria; GPI, glycophosphatidylinositol; LDH, lactate dehydrogenase; ULN, upper limit of normal; AA, aplastic anaemia; MDS, myelodysplastic syndrome; BMT, bone marrow transplant
Notes:
*Clinical indicators of PNH include:

- Intravascular haemolysis as evidenced by hemoglobinuria or elevated plasma haemoglobin
- Evidence of unexplained haemolysis with accompanying: iron deficiency; abdominal pain or oesophageal spasm; thrombosis; granulocytopenia and/or thrombocytopenia; other acquired Coombs'-negative, non-schistocytic non-infectious haemolytic anaemia
- Thrombosis with unusual features: unusual sites, with signs of accompanying haemolytic anaemia; with unexplained cytopenia
- Evidence of bone marrow failure: suspected or proven aplastic or hypoplastic anaemia; refractory cytopenia with uni-lineage dysplasia; other cytopenias of unknown aetiology after adequate workup

C.3 MANAGEMENT OF PNH

There are three major approaches to the treatment of PNH: supportive treatments, treatment changing the course of the disease, and potentially curative treatment.[22]

Supportive treatments focus on the symptoms of the disease and include blood transfusion, iron supplementation, steroids, anticoagulants, and immunosuppressive treatments. These treatments may be used in addition to eculizumab.

The only treatment capable of changing the course of the disease is eculizumab (Soliris®), which is listed on the LSDP. In Australia, eculizumab is indicated for the treatment of PNH and atypical Haemolytic Uraemic Syndrome (aHUS). The indication for PNH is subsidised under the LSDP, while the listing for aHUS is subsidised under the PBS. Eculizumab was registered by the TGA in 2009 and was made available on the LSDP in 2011.

Eculizumab is a humanised monoclonal antibody developed from mice. The drug is administered in adults and children at the same dosage consisting of an initial phase of 600mg administered via 25-45 minute intravenous infusions every week for 4 weeks, followed by a maintenance phase of 900mg administered via 25-45 minute intravenous infusion every 14 ± 2 days. Lower dosages are recommended for patients with a body weight of ≤ 40 kg.[24]

Table C-3 summarises the LSDP-funded medicine used for PNH management including units/vial, date of listing and sponsor.

Table C-3: LSDP-subsidised treatment for PNH

Medicine	mg / vial	Date of listing	Sponsor
Eculizumab (Soliris®)	300	1/01/2011	Alexion

The only potentially curative treatment for PNH is allogeneic bone marrow transplantation.[21] However it is associated with significant morbidity and mortality, which is why it is only recommended for patients resistant to thrombo-prophylaxis and eculizumab treatment who experience recurrent thromboembolic events. Registry studies have reported a 2-year post-transplant survival rate of 56% and 10-year survival rate of 42%.[22]

APPENDIX D: POTENTIAL SEARCH TERMS

D.1 POTENTIAL SEARCH TERMS: TOR 1

ToR 1 involves a systematic review of peer-reviewed papers and grey literature. As part of the systematic review, various data sources and databases will be examined to search for relevant evidence. The following search terms will be used for the systematic review in ToR 1:

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome") 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 filters[10] were consulted for this ToR. Below is the PubMed search string used for this ToR:

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome") AND (Patient OR Paediatric) 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**, eculizumab 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 PNH, Product information documents for PNH medicines on the ARTG, AIHW National Death Index data and Cause of Death data, and PNH registry data reports).

Table D-1: Search terms for Medline (via PubMed) ToR 3, eculizumab to placebo.≠

#	Search terms	Number of citations
#1	Randomized controlled trial [Publication Type]	481,259
#2	Controlled clinical trial [Publication Type]	569,450
#3	Randomized [Title/Abstract]	476,729
#4	Placebo [Title/Abstract]	202,620

#	Search terms	Number of citations
#5	Drug therapy [MeSH Subheading]	2,102,420
#6	Randomly [Title/Abstract]	310,193
#7	Trial [Title/Abstract]	545,334
#8	Groups [Title/Abstract]	1,932,299
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	4,487,190
#10	Animals [MeSH Terms] NOT Humans [MeSH Terms]	4,573,450
#11	#9 NOT #10	3,885,300
#12	Paroxysmal Nocturnal Haemoglobinuria [MeSH Terms]	3,357
#13	Paroxysmal Nocturnal Haemoglobinuria	4,057
#14	Paroxysmal Haemoglobinuria	3,957
#15	#12 OR #13 OR #14	4,070
#16	eculizumab [All Fields]	1,472
#17	eculizumab [Supplementary Concept]	808
#18	Soliris [All Fields]	1,472
#19	Alexion AND monoclonal antibody	107
#20	#16 OR #17 OR #18 OR #19	1,536
#21	#11 AND #15 AND #20	**225**

Abbreviations: MeSH, medical subject headings;
Note: Date of search for reproducibility 24 April 2019

D.4 POTENTIAL SEARCH TERMS: TOR 4

ToR 4 involves a systematic review of peer-reviewed papers and grey literature. As part of the systematic review, various data sources and databases will be examined to search for relevant evidence. The following search terms will be used for the systematic review in ToR 4:

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome") AND ("patient centred outcome" OR "patient centered outcome" OR "patient reported outcome" OR "patient related outcome" OR "patient outcome" OR "self-reported")

D.5 POTENTIAL SEARCH TERMS: TOR 5

For the search of economic evaluations:

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome")
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:

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome")
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 hql[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

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome")
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
(eculizumab OR soliris)

D.7 POTENTIAL SEARCH TERMS: TOR 7

("Paroxysmal Hemoglobinuria" OR "Paroxysmal Haemoglobinuria" OR "Paroxysmal Nocturnal Hemoglobinuria" OR "Paroxysmal Nocturnal Haemoglobinuria" OR "Haemoglobinuria, Paroxysmal Nocturnal" OR "Hemoglobinuria, Paroxysmal Nocturnal" OR "Haemoglobinuria, Nocturnal Paroxysmal" OR "Hemoglobinuria, Nocturnal Paroxysmal" OR "Marchiafava-Micheli Syndrome") 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 PNH.

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): CADTH Health Technology Update CADTH Issues in Emerging Technology	https://www.cadth.ca/ https://www.cadth.ca/reports?keywords=&product_type%5B%5D=107327&sort=field_date%3Avalue-desc&amount_per_page=10&email_address=&page=1 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.ncchta.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) FDA Office of Orphan Drugs Development	http://www.fda.gov/default.htm 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/

Data source	Website
PR Newswire	https://www.prnewswire.com/
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 PNH 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 PNH? • If yes, what is the official indication?				
Approved for PNH in Australia? • 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				