Summary of changes to draft Review Protocol for Gaucher disease medicines on the Life Saving Drugs Program (LSDP)

Background

On March 8 2019, the LSDP Expert Panel discussed the draft Review Protocol for Gaucher disease including the outcomes from the Gaucher disease Stakeholder Forum (held in Sydney on 22 February 2019).

Note that a Stakeholder Forum was also held for Fabry disease medicines. If changes suggested at that Forum were considered relevant to the Review Protocol for Gaucher disease medicines, the changes will be included (and vice versa).

General discussion

1. The Panel noted that four Panel members attended the Gaucher stakeholder forum. The Panel acknowledged that the feedback from the Stakeholder Forum was informative to the draft Review Protocol.

2. The Panel noted there were no significant changes to the draft Review Protocol.

3. The Panel noted that stakeholders would benefit from some background information to the purpose of the Research Protocol at the beginning of the document. Introductory comments to each Term of Reference (ToR) should also be included to provide context to what the purpose of each ToR is. The Panel agreed and recommended these be included.

4. The Panel noted that there had been discussion at the Stakeholder Forum around presenting ToR 6 (utilisation) as the first ToR in the Review Protocol. The Panel noted that whilst the Review Protocol document was set out to align with the order of the endorsed ToRs, it was not indicative of the importance of each ToR or how it will be presented in the draft and final reports. This also applies to the order of the research questions for each ToR.

Individual ToRs

ToR 1 – Review the prevalence of Gaucher disease within Australia.

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
No change required to draft research questions but there should be a general discussion in the draft report that whilst true prevalence will be difficult to ascertain, estimates can be obtained through various data sources.	The Panel recommended that a discussion of different methods of diagnosis, double counting if using multiple datasets, and multiple manifestations of Gaucher disease be considered in the analysis presented in the draft report.	2.8 LIMITATIONS p6 2.7 SYNTHESIS OF FINDINGS p. 6	The limitation with these datasets includes potential double counting and/or duplication captured by multiple diagnostic laboratories. The true prevalence of Gaucher disease may be difficult to ascertain however estimates can be obtained through various data sources. Additional data sources provide prevalence estimates by proxy however under and over reporting of prevalence should be considered when analysing of results.
Add an additional question "What proportion of Gaucher disease patients are eligible for the LSDP?"	To be included.	2.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 1 ToR 1 research questions Q2 p.3	2. What proportion of patients with Gaucher disease are eligible to access treatment under the LSDP?
If ToR 2 suggests eligibility criteria should change, add additional question to ToR 1: "What proportion of Gaucher disease patients would be eligible for the LSDP if eligibility criteria is modified?"	Panel noted it will be difficult to obtain data on prevalence at this level.	2.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 1 ToR 1 research questions Q5 p.3	5. What proportion of Fabry disease patients would be eligible for the LSDP if eligibility criteria is modified?
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**

Include Clinical Advisory Group (CAG) and other treating physicians.	The Panel noted clinicians could provide information on the number of patients with Gaucher disease in Australia and on the number enrolled in clinical trials.	2.6 STAKEHOLDER CONSULTATIONS p. 5	Expert opinion, will be sought from clinicians and peak consumer organisations, to inform factors affecting disease prevalence in Australia… and number of patients enrolled in clinical trials.
Include abstracts and conference proceedings/posters.	To be included.	2.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 1 (Table 2.2) p. 4	Literature search criteria for ToR 1. Search period. Conference abstracts published since 2017

ToR 2 - Review evidence for the management of Gaucher disease and compare to the LSDP treatment guidelines, patient eligibility and testing requirements for the use of these medicines on the program (including the validity of the tests).

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Change wording in Q1 from *treatment* to *management*.	Wording to be changed.	3.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 2 Research questions to address ToR 2. Q1 p. 8	1. What is the current best practice model for the diagnosis and management of Gaucher disease (i.e. adult and paediatric)? What is the quality of evidence underpinning this approach?
Consider adult and paediatric patients separately for Q1.	The Panel agreed with this change.	3.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 2 Research questions to address ToR 2 Q1 p. 8	1. What is the current best practice model for the diagnosis and management of Gaucher disease (i.e. adult and paediatric)? What is the quality of evidence underpinning this approach?
Consider splitting Q2 into two questions as eligibility criteria for initial access and ongoing access are different.	The Panel noted that HealthConsult plans to answer Q2 in the draft report in two steps - by considering initial eligibility criteria and	3.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 2 Q.2 p. 8	2. What are the eligibility criteria for initial and ongoing access to LSDP medicines?

	then ongoing eligibility criteria. It was not necessary to create two separate questions for the Review Protocol.		What is the quality of evidence underpinning these requirements?
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Include clinicians and patients as data sources.	The Panel noted that in a rare disease such as Gaucher, the lack of evidence from clinical studies means that clinical opinion has more prominence. Change wording from *if required* to *is required* and remove wording *if higher levels cannot be identified*.	3.4 STAKEHOLDER CONSULTATION p. 10	Stakeholders, including clinicians, clinical advisory group (CAG) clinicians and Gaucher Association of Australia & New Zealand
For the systematic literature review - broaden date restriction and include abstracts and conference proceedings/posters.	To be included with a limit of 2 years.	3.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 2 Search period. p. 9	Conference abstracts published since 2017
The search period for publications should go back 20 years.	The Panel noted that although the pivotal trials may be valuable in some contexts, to address current best practice, only up-to-date literature is required. Additional relevant literature may be identified by manual search of reference lists.	3.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 2 Search period p. 9	Articles published from 1999
The analysis should be split into pre-2014 and post-2014 due to the disbandment of the Gaucher Disease Advisory Committee (GDAC).	The Panel noted that HealthConsult will take this into consideration during analysis.	3.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 2 Search period p. 9	Analysis to be split into pre-2014 and post-2014

<u>ToR 3 - Review clinical effectiveness and safety of medicines and evaluate the evidence of comparative effectiveness of LSDP Gaucher disease medicines. This will include analysis of LSDP patient data and international literature to provide evidence of life extension.</u>

Suggested change to research questions	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Reword Q9 to include stabilisation of disease progression as well as extension of life.	The Panel noted that life extension is a compulsory criterion for a medicine to be included on the LSDP. However, Q9 can be broadened to include	4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3 ToR 3 research questions Q.5	4. Is there evidence that the Gaucher disease medicines have stabilised disease progression

	stabilisation of disease as it is a major goal of patient management.	p. 11	and/or extended survival?
Modify section 4.5 'Synthesis of Findings' to include stabilisation of disease progression.	To be included.	4.5 SYNTHESIS OF FINDINGS p.16	Stabilised disease progression and/or life extension research questions 5 and 6 will be informed by the systematic literature review on the natural history of Gaucher disease (Type 1) and stabilised disease progression and/or mortality/survival, analysis of LSDP patient-level data and LSDP medication duration.
If any changes to best practice are identified in ToR 2, effectiveness and safety should be examined in this new population.	To be included.	4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3 Q7-10 p. 11-12	7. What is the effectiveness and safety of imiglucerase in alternate eligible populations? 8. What is the effectiveness and safety of velaglucerase in alternate populations? 9. What is the effectiveness and safety of taliglucerase in alternate populations? 10. What is the effectiveness and safety of imiglucerase, velaglucerase and taliglucerase compared to each other in alternate populations?
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Stakeholder consultation is required.	The Panel noted that this ToR will be analysing LSDP patient	N/A	N/A

	data for evidence of life extension. Stakeholder consultation is not required for this ToR.		
Include abstracts and conference proceedings/posters.	These are to be included in updated review protocol as supplementary high-level data.	4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3 Literature search criteria for ToR 3 p. 13	Conference abstracts published since 2017
The analysis should be split into pre-2014 and post-2014 due to the disbandment of the Gaucher Disease Advisory Committee (GDAC).	The Panel noted that the purpose of the analysis is to determine the current safety and effectiveness and compare this to what was anticipated at the time the medicines were first included on the LSDP. HealthConsult will take into account the GDAC when analysing the data.	4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3 Literature search criteria for ToR 3 p. 13	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 Analysis to be split into pre-2014 and post-2014
Include clinical study reports.	The Panel recommended that these be requested from the sponsors.	4.2 SYSTEMATIC LITERATURE REVIEW p. 14	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, sponsors of the medicines included on the LSDP will be invited to provide unpublished clinical study reports (CSRs) relating to any potentially relevant trials.

ToR 4 - Review relevant patient based outcomes that are most important or clinically relevant to patients with Fabry disease.

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Consider paediatric and adult patients separately for both research questions.	To be included.	5.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 4 Research questions to address ToR 4 p. 17	1. What outcomes are most important to paediatric and adult patients who are being treated with LSDP medicines for Gaucher disease (Type 1) and their clinicians? 2. How can administration of the LSDP be improved (within reason) to help patients with Gaucher disease (Type 1) and their clinicians? Does the administration need to be different for paediatric and adult patients?
Consider how administration of the LSDP could be improved for paediatric and adult patients separately, patients and clinicians separately, and patients accessing the LSDP at different stages of their disease.	To be included.	5.5 SYNTHESIS OF FINDINGS p. 19	In addressing the research questions, attempts will be made to stratify patients (where appropriate) by: age, gender, location of infusion (e.g. hospital, home or self-administered), and/or severity/ disease progression.
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Include the new Gaucher-specific patient-reported outcome measure.	To be included.	5.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 4 Other means to identify evidence	or Gaucher specific PRO tools (Note: This is not validated; has been content validated only. Next step: psychometric validation)

Include the ICGG registry as a relevant data source.	To be included.	5.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 4 Other means to identify evidence	Clinician input and Clinician international sponsor registry data (e.g. ICGG Gaucher Registry)
Include sponsors as a data source.	To be included.	5.4 STAKEHOLDER CONSULTATIONS p. 18	HealthConsult intend to consult with (i) consumers and/or consumer advocacy groups (e.g. Gaucher Association of Australia & New Zealand), (ii) clinicians and (iii) sponsors
LSDP patient-level data will not inform Q1.	The Panel noted that the reason for including this data source needs better clarification in the protocol. Quality of life in the LSDP patient-level data may correlate with changes in treatment or other events captured in the data. Data will be used as an introduction to patient focus groups.	5.3 LSDP PATIENT-LEVEL DATA p. 18	The LSDP patient-level data contains patient monitoring and outcomes data related to the quality of life whilst on ERT. This data source will provide both the data and the domains or measures of quality of life (from PRO measures or PROM tools) that will be cross-referenced with findings from the ToR 4 systematic review and stakeholder consultations to address research question 1.
Include online surveys as a method of obtaining data more broadly from patients who cannot attend a focus group.	Some stakeholders may find teleconferences or online surveys preferable to face-to-face meetings therefore the Panel recommended they be included.	5.4 STAKEHOLDER CONSULTATIONS p. 18	may include focus groups, an online survey, teleconference, webinar(s) and/or one-on-one interviews (by telephone, face-to-face and/or via videoconference).

ToR 5 - Conduct an analysis of the value for money of LSDP Gaucher disease medicines under the current funding arrangements.

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Include a new research question comparing the cost-effectiveness now versus when the program started in 1999.	The Panel noted that this information would be informative; however, there were no formal cost-effectiveness analysis models presented in the original PBAC submissions for these older medicines. Comparisons will be made between the expectations at the time of funding and now.	6.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 5 Research questions to address ToR 5	1. What is the total annual cost of treating a patient with the LSDP medicines? Is this different to what was expected at the time these medicines were included on the LSDP (e.g. actual vs predicted)? 2. What difference in quality of life is estimated for successfully treated and untreated patients with Gaucher disease? Is this different to what was expected at the time these medicines were included on the LSDP (e.g. actual vs predicted)? 3. What difference in survival is estimated for successfully treated and untreated patients with Gaucher disease? Is this different to what was expected at the time these medicines were included on the LSDP (e.g. actual vs predicted)?
Add a research question that focuses on the total cost of Gaucher disease, including indirect costs, to capture patient burden.	The Panel noted that indirect costs and societal perspective economic evaluations are not generally accepted by PBAC. The Panel recommended it be added as narrative to the draft report but inclusion in an economic model is out of scope.	6.9 SYNTHESIS OF FINDINGS p. 23	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.
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Baseline quality of life would need to be obtained through stakeholder consultation.	The Panel considered that stakeholder consultation for quality of life will be undertaken if estimates cannot be found in the literature.	6.8 STAKEHOLDER CONSULTATION (IF REQUIRED) p. 23	If values for inputs to the economic evaluation cannot be sourced from evidence from higher levels in the hierarchy of evidence (as described in Sections 6.2 to 6.7), expert opinion will be sought
Data sources for a societal perspective would need to be considered if a societal analysis is to be undertaken.	The Panel noted that indirect costs and societal perspective economic evaluations are not generally accepted by PBAC. The Panel recommended it be added as narrative to the draft report but inclusion in an economic model is out of scope.	6.9 SYNTHESIS OF FINDINGS p. 23	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.
Include registry data.	HealthConsult to request aggregated data (summary data) from sponsors to inform research questions.	6.8 STAKEHOLDER CONSULTATION (IF REQUIRED) p. 23	Expert opinion may include data obtained through surveys undertaken by

			Gaucher Association of Australia & New Zealand and/or CAG/clinician international sponsor registry aggregate data.
Include clinicians and patients.	The Panel noted these groups will be consulted should the information required to inform the economic evaluation not be available from other sources.	6.8 STAKEHOLDER CONSULTATION (IF REQUIRED) p. 23	If values for inputs to the economic evaluation cannot be sourced from evidence from higher levels in the hierarchy of evidence (as described in Sections 6.2 to 6.7), expert opinion will be sought.
Include abstracts and conference proceedings/posters.	To be included but limited to conference abstracts published since 2017.	6.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 5 p. 21	Conference abstracts published since 2017

ToR 6 - Review the utilisation of LSDP Gaucher disease medicines, including the way they are stored and dispensed, and evidence of patient compliance to treatment.

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Include a question asking where are the treatments administered (home, hospital, clinic etc.)?	The Panel noted that the utilisation analyses could include looking at location of administration. A separate research question was not required, but the information could be included as part of the draft report.	7.8 SYNTHESIS OF FINDINGS p. 28	If data is available the treatment setting (e.g. home, hospital etc) in which administration of the LSDP medicine occurs and/or postcode of the location where administration occurs and/or home postcode of patient will be analysed to assess if any of these variables have an impact on medicine utilisation and/or compliance.

Include a new question asking whether the location of infusion has an impact on therapeutic efficacy.	The Panel noted that it is unlikely that the location of the infusion has an impact on whether the medications are working or not. The location may have an impact on compliance, which is examined in existing research questions for this ToR.	7.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 6 Compliance questions 8-12 p. 26 7.8 SYNTHESIS OF FINDINGS p. 28	Compliance questions 8-12 If data is available the treatment setting (e.g. home, hospital etc) in which administration of the LSDP medicine occurs and/or postcode of the location where administration occurs and/or home postcode of patient will be analysed to assess if any of these variables have an impact on medicine utilisation and/or compliance.
Include a new question asking whether the geographic state, the type of treating centre, or metro/regional split have an impact on utilisation.	The Panel noted that the LSDP patient data that will be provided to HealthConsult is de-identified. The inclusion of personal information such as postcode may jeopardise the unidentifiable nature of the data. The Panel also discussed that breaking the data down to a geographical level was an immense undertaking, particularly given the length of time these medicines have been available on the program. The Panel was uncertain if such an analysis would be informative and therefore did not recommend that this research question be added.	7.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 6 Compliance questions 8-12 p. 26 7.8 SYNTHESIS OF FINDINGS p. 28	Compliance questions 8-12 If data is available the treatment setting (e.g. home, hospital etc) in which administration of the LSDP medicine occurs and/or postcode of the location where administration occurs and/or home postcode of patient will be analysed to assess if any of these variables have an impact on medicine utilisation and/or compliance.

Suggested change to data sources	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Remove text related to antibodies to treatment from the section on LSDP patient-level data because monitoring of antibodies is not relevant in Gaucher disease.	The Panel noted the advice of the CAG members at the Forum that the development of antibodies does not influence the efficacy of the medicines. Text to be removed in the Review Protocol.	7.3 LSDP PATIENT-LEVEL DATA	The level of substrates and clinical indicators of disease severity may be included in clinical notes.
Include abstracts and conference proceedings/posters.	To be included but limited to conference abstracts published since 2017.	7.2 SYSTEMATIC LITERATURE AND DOCUMENTATION REVIEW Literature search criteria for ToR 6 p. 26	Conference abstracts published since 2017

ToR 7 - Investigate developing technologies that may impact future funded access.

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Include a research question on the potential impact of any identified technologies on patient quality of life.	The Panel noted that while new technologies could potentially improve patient quality of life, the analysis of this outcome would be premature given the technologies could be years away from implementation. Potential impact could form part of the discussion in the draft report.	8.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 7 p. 30 8.9 SYNTHESIS OF FINDINGS p. 33	and what impact (if any) this could have on the administration of the program going forward. 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.
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Include abstracts and conference proceedings/posters.	Abstracts/conference proceedings will be included as supplementary high-level data.	8.2 PEER-REVIEWED LITERATURE P. 31	Conference abstracts published since 2017
Stakeholder consultation should be included.	The Panel noted that although stakeholders such as clinicians and sponsors would be aware of new developments, any	N/A	N/A

	technologies which are not confidential would be accessible through the data sources identified.		
The time period that we are expecting the new technology to arrive in should be defined.	A 5-year time horizon allows for a reasonable scope to the analysis while focusing on technologies which may impact the LSDP in the near future, as opposed to technologies in very early stages of development which have a higher failure rate.	8.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 7 p. 30	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 LSDP Gaucher disease medicines will be undertaken.