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

Background

On March 8 2019, the LSDP Expert Panel discussed the draft Review Protocol for Fabry disease including the outcomes from the Fabry disease Stakeholder Forum (held in Melbourne on 21 February 2019).

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

General discussion

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

2. The Panel noted there were no significant changes recommended to the 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 Fabry 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 noted that under and over reporting of prevalence discussion should be considered in the analysis and draft report.	2.8 LIMITATIONS p7 2.7 SYNTHESIS OF FINDING p. 7	The limitation with these datasets includes potential double counting and/or duplication captured by multiple diagnostic laboratories. The true prevalence of Fabry 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 Fabry 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.4	2. What proportion of patients with Fabry 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 Fabry 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.4	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 Fabry Australia.	Change wording from *may be* used to *will be* used.	2.6 STAKEHOLDER CONSULTATIONS p. 6	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 ANZ (Australia and New Zealand Dialysis and Transplant Registry) data.	To be included.	2.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 1 (Table 2.2) p. 5	Literature search criteria for ToR 1. Other means to identify relevant information. ANZDATA
Include abstracts and conference proceedings/posters.	To be included.	2.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 1 (Table 2.2) p. 5	Literature search criteria for ToR 1. Search period. Conference abstracts published since 2017

<u>ToR 2 - Review evidence for the management of Fabry 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).</u>

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. 9	1. What is the current best practice model for the diagnosis and management of Fabry 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 then ongoing eligibility criteria. It was not necessary to create two separate questions for the Review Protocol.	3.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 2 Q.2 p. 9	2. What are the eligibility criteria for initial and ongoing access to LSDP medicines? 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 the CAG as a data source.	Make the wording more explicit that CAGs are included in the "Stakeholder consultation".	3.4 STAKEHOLDER CONSULTATION p. 11	Stakeholders, including clinicians, clinical advisory group (CAG) clinicians and Fabry Australia, will be approached
Change wording from *if required* to *is required*. Remove wording *if higher levels cannot be identified*.	The Panel noted this was included in error. A key data source will be stakeholder consultation for this ToR.	3.4 STAKEHOLDER CONSULTATION p. 11	The use of expert opinion to address the research questions in the review
Include Fabry Australia as a data source.	Make the wording more explicit that Fabry Australia is included in the "Stakeholder consultation".	3.4 STAKEHOLDER CONSULTATION p. 11	Stakeholders, including practicing clinicians, clinical advisory group (CAG) clinicians and Fabry Australia
For the systematic literature review - broaden date restriction and include abstracts and conference proceedings/posters.	To be included.	3.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 2 Search period p. 10	Conference abstracts published since 2017
The Medical Advisory Committee of Fabry Australia to be used as a primary source and not secondary.	Fabry Australia clinicians will likely be the same clinicians as the CAGs. HealthConsult to work with Fabry Australia to ensure their clinicians are invited to have input.	3.4 STAKEHOLDER CONSULTATION p.11	Stakeholders, including practicing clinicians, clinical advisory group (CAG) clinicians and Fabry Australia, will

<u>ToR 3 - Review clinical effectiveness and safety of medicines and evaluate the evidence of comparative effectiveness of LSDP Fabry 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 together with 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 stabilisation of disease.	4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3 ToR 3 research questions Q.4 p. 12	4. Is there evidence that the Fabry disease medicines have stabilised disease progression 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 4 and 5 will be informed by the systematic literature review on the natural history of Fabry disease and stabilised disease progression and/or mortality/survival, analysis of LSDP patient-level data and LSDP medication duration.
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Include CAG as a data source.	The Panel noted that this ToR will be analysing LSDP patient data for evidence of life extension. Stakeholder consultation is not required for this ToR.	N/A	N/A
Include international sponsor registries as a data source.	These may provide additional clinical efficacy and safety information.	4.1 OVERVIEW OF DATA SOURCES TO INFORM TOR 3 PICO supporting ToR 3 p. 13	Fabry disease registry and FOS published registry data reports
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. 14	Conference abstracts published since 2017
LSDP dispensing data - 'Reduced doses' is mentioned in paragraph 2. This needs to also include shortages of treatment.	Wording to be updated.	4.6 LIMITATIONS p. 17	Impact of stock shortages and forced switching protocols.

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

Suggested change to research questions	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Include examples in Q1 of what the types of outcomes may be	The Panel noted that this may be leading the stakeholders	N/A	N/A

(e.g. family, fatigue, school, work, activities and carers).	and recommended it not be included in the Review Protocol. HealthConsult to include these examples in its introduction to the focus groups.		
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
Include international sponsor registry data.	The Panel recommended that it be included in the Research Protocol but noted aggregate data may be obtainable but patient level data is unlikely. In other words, the data that would be provided would likely not be for specific individuals but as more of an overall summary.	5.2 SYSTEMATIC LITERATURE REVIEW p. 19 5.6 LIMITATIONS p. 20	Clinician input and Clinician international sponsor registry data Requested CAG and clinician international sponsor registry data may obtain aggregate data but patient level data is unlikely.
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. 19	The gathering of stakeholder input 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).
Include abstracts and conference proceedings/posters.	To be included.	5.2 SYSTEMATIC LITERATURE REVIEW Literature search criteria for ToR 4 p. 19	Conference abstracts published since 2017
Change wording in Section 5.4 on page 20 in 'Stakeholder Consultations' that outcomes identified through the systematic literature review and LSDP patient level data *may be* presented to patients and clinicians during stakeholder forums to gain their feedback.	To change wording from *may be* to *will be*.	5.4 STAKEHOLDER CONSULTATIONS p. 20	Stakeholder consultations will begin with a presentation of patient reported outcomes identified in the literature review and LSDP patient-level dataset.

<u>ToR 5 - Conduct an analysis of the value for money of LSDP Fabry disease medicines under the current funding arrangements.</u>

Suggested change to research questions	Expert Panel recommendation	18/03/2019 Section/page	Relevant section of protocol
Add a research question that focuses on the total cost of Fabry 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 but inclusion in an economic model is out of scope.	6.9 SYNTHESIS OF FINDINGS p. 24-25	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**
Include International sponsor registry data.	HealthConsult to request aggregated data (summary data) from sponsors to inform research questions.	6.8 STAKEHOLDER CONSULTATION (IF REQUIRED) p. 24	international sponsor registry aggregate data.
Include CAG and Fabry Australia.	The Panel noted these groups were intended to be consulted as part of the stakeholder consultation but recommended that this be made explicit in the Review Protocol.	6.8 STAKEHOLDER CONSULTATION (IF REQUIRED) p. 24	The collection and reporting of expert opinion from patients and clinicians will be conducted and/or CAG/clinician
Include ANZ (Australia and New Zealand Dialysis and Transplant Registry) data.	To be included.	6.8 STAKEHOLDER CONSULTATION (IF REQUIRED) p. 24	data from the ANZDATA (including pre-2002 or kidney function at time of starting LSDP compared to projection with ANZDATA)
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. 22	Conference abstracts published since 2017

ToR 6 - Review the utilisation of LSDP Fabry 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
No additional questions suggested.	The Panel noted that the issues raised in general discussion at the Stakeholder Forum can be addressed with current research questions.	N/A	N/A
Suggested change to data sources	**Expert Panel recommendation**	**18/03/2019 Section/page**	**Relevant section of protocol**
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. 27	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
Move Q2 ("What new patient testing methodologies are being developed/adopted/promoted?") to ToR 2.	The Panel considered that Q2 is not applicable to ToR 2.	N/A	N/A
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. 32	Conference abstracts published since 2017