Australian Government

Department of Health

Post-market review of the Life Saving Drugs Programme

June 2014 – June 2015

Report to the Australian Government

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Structure of the report

This report is presented in eight parts, as briefly outlined below. The report structure is designed to lay out how the review was conducted, who was consulted, the issues that were identified, stakeholders' input and the deliberations of the independent expert reference group in making its recommendations to government.

Section 1 – Life Saving Drugs Programme Post Market Review terms of reference.

Section 2 – Chronology of the review process, stakeholder consultations, industry briefings and lists of all the submissions received.

Section 3 – Life Saving Drugs Programme Reference Group recommendations.

Section 4 – Overview of the processes undertaken during the review.

Section 5 – Description of issues that emerged after the programme review in 2008–2009 and the revision of the funding criteria in 2010.

Section 6 – Reference group issues paper and stakeholder views.

Section 7 – Reference group consideration of responses received and its conclusions.

Section 8 – Proposed steps to transition the Life Saving Drugs Programme into a Medicines for Rare Diseases Programme.

Membership of the Life Saving Drugs Programme Reference Group

Professor Andrew Wilson – Chair

Professor David Sillence – Clinical Expert

Professor David Isaacs – Clinical Expert

Professor Anne Tonkin – Clinical Expert

Professor Jane Hall – Health Economist

Professor Paul Komesaroff – Medical Ethicist

Mrs Lesley Murphy – Consumer Representative, Rare Voices Australia

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Section 1: Life Saving Drugs Programme Post Market Review terms of reference

1. Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.
2. Review emerging clinical treatments and diseases, including those that identify subgroups by molecular target, which could potentially seek subsidisation through the LSDP in the future.
3. Conduct an international comparison of subsidisation of medicines for rare diseases and the definitions for a rare/ultra-rare disease.
4. Compare the subsidisation and equity principles of the Pharmaceutical Benefits Scheme and the LSDP.
5. Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug's treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.
6. Review the administration of the LSDP, including the Guidelines with which the programme is administered for each condition, and assess alternative administration systems.
7. Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.

Section 2: Chronology of the Life Saving Drugs Post Market Review

Table 1: Chronology of announcements, stakeholder meetings and other events

Events and consultations	Timelines and consultation periods	Length of consultations	Numbers of attendees at meetings and submissions received
Consultation on draft terms of reference	August 2013	2 weeks	16
Public announcement of the review	9 April 2014		
Establishment of the LSDP Reference Group	June 2014		
Reference group 1st meeting	8 August 2014		
Reference group teleconference (2nd meeting)	14 August 2014		
Consultation on terms of reference	11 August 14 – 10 November 2014	3 months	31 submissions received
Rare Voices Australia facilitated consultation on the review[a]	5 September 2014		20 attendees
Reference group 3rd meeting	16 December 2014		
Reference group 4th meeting	2 February 2015		
Submissions to terms of reference published	4 March 2015		
Consumers Health Forum facilitated workshops on terms of reference 4 and 7[b]	19 March 2015 (Melbourne) 24 March 2015 (Sydney)		50 attendees (excluding facilitators)
Consumers Health Forum online survey	19 March 2015 – 10 April 2015		174 respondents
Issues paper published	10 April 2015 – 30 April 2015	Approx. 3 weeks	28 submissions received
LSDP technical assessment report published	10 April 2015		
Issues paper – 1st extension[c]	Up to 4 May 2015		

Invitation to Rare Voices Australia to meet the reference group	30 April 2015		Invitation declined
Reference group 5th meeting	6 May 2015		
Reference group industry briefing	6 May 2015		14 industry attendees
Issues paper – 2nd extension[d]	Up to 18 May	5 weeks	30 submissions received
Rare Voices meeting with reference group chair	8 May 2015		
Rare Voices and patient organisation leaders meeting with reference group chair and consumer representatives	20 May 2015		8 patient representatives attended
Reference group letter to consumers	26 May, 2 & 3 June 2015		
Revised industry proposal received	10 June 2015		
Reference group 6th meeting	20 July 2015		
Final report	August 2015		

a Attended by the Department of Health.

b Consumers Health Forum workshops were held in Melbourne and Sydney. The workshops were attended by one reference group member and departmental staff.

c Consumers Health Forum, Rare Voices, Australian Medical Association, Medicines Australia and Pfizer requested and were granted an extension.

d Consultation period extended to all.

Table 2: List of submissions in response to the review terms of reference

Submitter	Date received
1. Health professional	23 Sep 2014
2. Dr James Gray	5 Oct 2014
3. Consumer	24 Oct 2014
4. Professor Jeffrey Szer	26 Oct 2014
5. Clinical Professor Jack Goldblatt	28 Oct 2014
6. Duchenne Foundation	4 Nov 2014
7. Australian Pompe's Association	5 Nov 2014
8. Fabry Support Group Australia	7 Nov 2014
9. BioMarin Pharmaceutical Australia	7 Nov 2014
10. Dr David Ketteridge	7 Nov 2014
11. Gaucher Association of Australia	7 Nov 2014
12. Pfizer Australia	9 Nov 2014
13. Carer	9 Nov 2014
14. Carer	9 Nov 2014
15. AstraZeneca	9 Nov 2014
16. uniQure Biopharma BV	10 Nov 2014
17. Shire Australia	10 Nov 2014
18. Non-government organisation	10 Nov 2014
19. Vertex Pharmaceuticals	10 Nov 2014
20. Rare Voices Australia	10 Nov 2014
21. Office of Population Health Genomics and Genetic Services (WA Department of Health)	10 Nov 2014
22. Consumer	10 Nov 2014
23. The McKell Institute	10 Nov 2014
24. Medicines Australia	10 Nov 2014
25. The Cancer Drugs Alliance	10 Nov 2014
26. Mucopolysaccharide & Related Diseases Society Australia Ltd	10 Nov 2014
27. Genzyme, A Sanofi Company	10 Nov 2014
28. Australasian Society of Inborn Errors of Metabolism	10 Nov 2014
29. GlaxoSmithKline	10 Nov 2014
30. Alexion Pharmaceuticals Australasia	11 Nov 2014
31. The Society of Hospital Pharmacists Australia	14 Nov 2014

Table 3: List of submissions in response to the reference group issues paper

Submitter	Date received
1. Health professional	13 Apr 2015
2. Professor Jack Goldblatt	16 Apr 2015
3. Karen & Steven Goodman	23 Apr 2015
4. Carer	27 Apr 2015
5. Professor Jeffrey Szer (endorsed by 8 ex-disease advisory committee members)	27 Apr 2015 (8 May 2015)
6. James Sterling	28 Apr 2015
7. The Society of Hospital Pharmacists Australia	28 Apr 2015
8. Consumer	28 Apr 2015
9. Medical Oncology Group of Australia	29 Apr 2015
10. The McKell Institute	29 Apr 2015
11. Australian Pompe's Association	29 Apr 2015
12. PNH Support Association of Australia	29 Apr 2015
13. Consumer	29 Apr 2015
14. Carer	29 Apr 2015
15. Consumer	29 Apr 2015
16. Sydney Children's Hospital Network Genetic Metabolic Disorders Service	30 Apr 2015
17. Non-government organisation	30 Apr 2015
18. Consumer	30 Apr 2015
19. Queensland Health	30 Apr 2015
20. Optum	30 Apr 2015
21. Carer	30 Apr 2015
22. Rare Voices Australia	30 Apr 2015
23. Consumer	30 Apr 2015
24. Consumer	30 Apr 2015
25. Fabry Support Group of Australia	30 Apr 2015
26. Genzyme, A Sanofi Company	30 Apr 2015
27. Royal Australian and New Zealand College of Ophthalmologists	30 Apr 2015
28. Consumer	30 Apr 2015
29. Consumer	1 May 2015
30. Vertex Pharmaceuticals	4 May 2015
31. Consumer	5 May 2015
32. Australian Medical Association	8 May 2015
33. Consumer	8 May 2015
34. Dr Janice Fletcher	8 May 2015

35. Consumer	9 May 2015
36. Consumer	12 May 2015
37. Shire Australia	14 May 2015
38. Biomarin Pharmaceutical Australia	15 May 2015
39. Consumer	15 May 2015
40. AstraZeneca	15 May 2015
41. Consumer	16 May 2015
42. Consumer	16 May 2015
43. Consumer	17 May 2015
44. Consumer	17 May 2015
45. Consumer	18 May 2015
46. Pfizer Australia	18 May 2015
47. Consumer	18 May 2015
48. Alexion	18 May 2015
49. Sanfillippo Children's Foundation	18 May 2015
50. Consumers Health Forum of Australia	18 May 2015
51. Mucopolysaccharide & Related Diseases Society Australia Ltd	18 May 2015
52. Consumer	18 May 2015
53. Dr David Ketteridge	18 May 2015
54. Consumer	18 May 2015
55. Australasian Society of Inborn Errors of Metabolism	18 May 2015
56. Consumer	18 May 2015
57. Medicine Australia	18 May 2015
58. Consumer	18 May 2015
59. Cancer Drug Alliance	19 May 2015

Section 3: Life Saving Drugs Programme Reference Group recommendations

In providing advice to the Minister, the reference group recommends that:

1. The Commonwealth Government should continue to enable access to and provide funding for medicines to treat Australians with rare diseases, where those medicines have been evaluated for safety, efficacy and clinical effectiveness.

The reference group received many submissions maintaining that the mechanism of access to medicines is not as relevant to patients as is the assurance that patients who are currently receiving treatment or may require future treatment will continue to receive treatment through a Government-subsidised programme.

2. Medicines currently included on the Life Saving Drugs Programme (LSDP) should be grandfathered to a new Medicines for Rare Diseases Programme (MRDP) to ensure existing and new patients who meet eligibility criteria and who continue to benefit from receiving treatment for diseases currently funded under the LSDP will continue to be supported.

It is the view of the reference group that subsidy of the medicines listed below for the 268 eligible existing patients on the LSDP should be ongoing for as long as the medicine is safe and needed and remains effective.

- Imiglucerase (Cerezyme®), Velaglucerase (VPRIV®) and Miglustat (Zavesca®) for the treatment of Gaucher disease (type 1)
- Agalsidase alfa (Replagal®) and Agalsidase beta (Fabrazyme®) for the treatment of Fabry disease
- Laronidase (Aldurazyme®) for the treatment of mucopolysaccharidosis type I (MPS I)
- Idursulfase (Elaprase®) for the treatment of mucopolysaccharidosis type II (MPS II)
- Galsulfase (Naglazyme®) for the treatment of mucopolysaccharidosis type VI (MPS VI)
- Alglucosidase alfa (Myozyme®) for the treatment of infantile-onset and juvenile late-onset Pompe disease
- Eculizumab (Soliris®) for the treatment of paroxysmal nocturnal haemoglobinuria (PNH)

In assessing the rationale for continuing the funding of these medicines, the reference group noted the evidence supporting the contention that these medicines improve both quantity and quality of life. It was noted that the rarity of these diseases means that the quality of evidence on their continuing effectiveness remains less than would usually be considered necessary for a Pharmaceutical Benefits Scheme (PBS) subsidy. This will be an ongoing problem for medicines for rare diseases and will need to be considered in developing the criteria for future entry into and continuation in any funding programme.

The medicines listed above should be listed on the PBS under the proposed Medicines for Rare Diseases Programme for subsidy purposes ('grandfathering' of the listing of the drug). Patients currently receiving these medicines should continue to receive them providing they meet the existing eligibility and continuation rules for access

('grandfathering' existing patient access). New patients should be able to access the medicines providing they meet eligibility criteria current at the time of their need.

3. The LSDP should be transitioned from a standalone programme and be formally established as a special programme under section 100 of the* National Health Act 1953*, mirroring other section 100 programmes such as the Highly Specialised Drugs Programme, to benefit from existing structures, processes and systems currently within the Pharmaceutical Benefits Scheme.

The reference group believes that, while a designated Medicines for Rare Diseases Programme is needed, it does not need to sit outside the PBS. The PBS has demonstrated agility in accommodating special needs medicine programmes through special provisions in the National Health Act. The reference group recommends that leveraging existing structures, processes and administrative systems within the PBS to provide medicines to patients with rare or ultra-rare diseases is an appropriate way forward. The reference group notes the preference of industry and some patient groups for a new special section 200 programme under the same Act. The Department of Health has advised that, subject to the establishment of an appropriate head of power, establishing a special arrangement under the provisions of section 100 of the National Health Act may incorporate all our other recommended changes, and is a simpler approach legislatively.

The reference group believes that either approach would meet the requirements and therefore recommends a section 100 Medicines for Rare Diseases Programme mirroring the section 100 Highly Specialised Drugs Programme.

4. The new programme should be known as the Medicines for Rare Diseases Programme. Eligibility criteria for consideration of listing under the new programme are proposed based on the current LSDP criteria. These new criteria should be reviewed in two years or after the first four submissions have been assessed using the new criteria (whichever comes first).

The reference group received representations from industry and patient groups about the conditions and criteria governing the LSDP and the existing PBS 'rule of rescue' conditions that guide the Pharmaceutical Benefits Advisory Committee (PBAC) in its decision making. The reference group concluded that the conditions and criteria shared some overlap. The announced review of the PBAC submission guidelines presents an opportunity to amalgamate these conditions and criteria and integrate them into the existing PBS-PBAC framework.

Drawing on this and the comments from stakeholders and industry the reference group proposes the following revised criteria for a medicine to be considered for listing under the proposed new Medicines for Rare Diseases Programme. Medicines would need to meet all of the criteria.

1. There is a rare but clinically definable chronic progressive disease for which the medicine is registered for that indication by the Therapeutic Goods Administration (TGA).
2. The disease is identifiable with reasonable diagnostic precision.
3. Epidemiological and other studies provide sound scientific evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from

the disease, or significant ongoing disability such that the patient would not live independently once the disease was fully manifest.

4. The PBAC considers that based on sound scientific evidence it is more likely than not that a patient's lifespan will be substantially extended or the level and duration of disability substantially reduced as a direct consequence of the use of the drug.
5. That it would not be practical to confirm this through further studies within five years because of the rarity and rate of progression of the disease.
6. There is no alternative medicine listed on the PBS or available for public hospital in-patients which can be used as effective treatment for the disease. However, the availability of an alternative medicine under the MRDP does not disqualify the proposed medicine from consideration for the MRDP.
7. There is no alternative non-medicine therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition.
8. The cost of the medicine, defined as the cost per dose multiplied by the expected number of doses in one year for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.
9. The sponsoring company demonstrates that it is undertaking an ongoing programme to clarify the clinical benefits or agrees to actively participate in and financially support such a program.

The reference group noted the concerns of patient groups and industry about defining 'rare'. This is addressed in Recommendation 7. The Reference Group also noted the concerns about the interpretation of what the PBAC would consider a significant or substantial reduction in life expectancy. However, there is a clear precedent established with the diseases for which medicines are now listed. Patient groups and industry submissions also expressed a desire to see reference to quality of life as well as reduced life expectancy. After consideration of the nature of conditions for which the programme was initially established, the reference group preferred the more explicit term 'disability'.

The Medicines for Rare Diseases Programme should incorporate a process to ensure that appropriate expert input is incorporated in the advice provided to the PBAC (see Recommendation 6). However, the PBAC would remain the body making any decisions regarding recommendations to the Minister for listing of medicines on the PBS.

5. There is a need when considering the value of medicines for rare diseases to consider matters beyond cost-effectiveness. These principles are already embedded in the approach used by the PBAC in its decision making but this would benefit from being more transparent.

In assessing a medicine for listing on the PBS, the PBAC considers a number of relevant factors beyond comparative cost-effectiveness, comparative health gain and financial implications for the PBS or the Government health budget. These factors comprise issues such as patient affordability, the presence of effective alternatives and the severity of the medical condition treated. The reference group believes that a greater and more explicit consideration of quality of life and long-term disability in rare diseases would be an important addition to this list of societal factors to balance a perceived focus on patient survival.

The reference group recommends that the Department of Health examine the merits of the UK National Institute for Health and Care Excellence Highly Specialised Technologies Programme. This should also include consideration of a more structured and transparent approach to consideration of broader health benefits.

6. Consideration should be given to enhancing the medicines submission process for rare disease therapies by adopting a collaborative multi-stakeholder approach early in the assessment cycle, before the medicine submission is formally submitted for consideration by the PBAC.

The present assessment pathway for a medicine for a rare disease requires the PBAC to first consider the medicine for listing on the PBS. Typically the medicine for a rare disease is highly priced and is rejected because it is not considered cost-effective. After the medicine is rejected for PBS listing, it is then considered for inclusion on the LSDP.

The reference group recommends a streamlined process involving formal information gathering from interested and relevant stakeholders for the disease type, relevant members of the PBAC and departmental staff prior to commencement of the formal PBAC evaluation process. Early discussion about the appropriateness of the medicine as a rare disease therapy, data requirements and potential initiation and stopping guidance for administering the medicine would provide a clearer path for submission and assessment. In this regard it is noted that the TGA recommends that the orphan drug designation process is initiated 2-3 months prior to the start of the registration process. Early identification of information gaps, the level of evidence available and what is required, through engagement with stakeholders, would ensure that the medicine submission and health technology assessment pathways are constructive and transparent to all stakeholders. This would imply early involvement of representatives of stakeholders at the pre-submission conference. The process will also promote transparency and could potentially achieve earlier community access to the drugs.

7. **'Rare disease' should be defined for the purpose of the Medicines for Rare Diseases Programme.**

For the purpose of the Medicines for Rare Diseases Programme, the Reference Group propose a definition of a prevalence of 1 per 50,000 (an approximate total of 500 prevalent cases per disease in the Australian population, for designating a medicine on the PBS for evaluation and listing.

The reference group notes that the majority of conditions treated through medicines funded by the LSDP currently are lysosomal storage diseases or disorders, which are ultra-rare conditions. The reference group also notes variations in numerical definitions of rare disease in different populations. The proposed definition for section 100 listing in the PBS would keep the prevalence of the diseases treated in this scheme in the ultra-rare disease category, maintaining the historical objectives of the LSDP scheme with some expansion of numbers.

This definition is aimed at single diseases with prevalence close to or equivalent to the total number of people whose medicines are funded by the LSDP. It is not intended to cover genetic subsets of diseases. This definition should be incorporated into the PBAC guidelines and revisited in two years' time.

The review also noted that:

1. Definitions based on a numerical frequency estimate in the Australian population are definable for very few disorders.
2. While overseas studies can give some guidance, the frequencies of rare genetic disorders vary considerably between populations here and overseas.
3. The best data for Australian populations is from newborn screening programmes, which can give a reliable estimate only for phenylketonuria, galactosaemia, cystic fibrosis, congenital hypothyroidism etc.
4. Several other sources of data can give population frequencies for rare genetic disorders, e.g. Huntington's disease, and some non-genetic disorders, e.g. multiple sclerosis.

For the purpose of public subsidy, the meaning of rare disease is restricted to the prevalence proposed. The medicine can only be classified as a rare disease treatment for a particular indication as registered by the TGA. Unlike the TGA's Orphan Drugs Programme, for the purposes of subsidising the medicine on the PBS section 100 Medicines for Rare Disease Programme, the medicine may be only classified as a rare medicine once.

8. A small number of centres of clinical expertise in rare diseases should be established. These should incorporate state-based clinical advisory committees, with the larger states networking with smaller states or territories.

The reference group notes that in relation to these medicines, as well as the funding mechanism there is a need for an efficient and effective distribution system. The conditions for which these medicines are being prescribed are managed by a small number of specialists. Consequently the reference group believes that having a small number of centres of expertise located across the states and territories would improve access to clinical care and patient management. Such centres could also provide support to patients and their usual treating clinician where they are managed away from the centre. It is likely that in most if not all cases these centres of clinical expertise would be a formal recognition of the role of existing treatment hubs.

Specialised treatment centres for Fabry disease are already operating in the states and territories and can be emulated across the different rare disease types. Setting these centres up across five states and territories may enable them to act as central nodes of clinical expertise and education for patients and professionals alike.

In the main, stakeholders supported establishing these centres. A few stakeholders were concerned that states and territories would not fund these centres as a matter of priority without central management. Others were concerned that, without a centrally managed programme, there is a risk that clinical expertise may be diluted over time. It is important to note that access to subsidy for these medicines would not be limited those treated at the centres of expertise but that these centres would have a critical role in monitoring the overall patient populations.

9. The Department of Health should support the development of a fit-for-purpose data collection framework and require sponsors of medicines for rare diseases to collect the data necessary to support initial and ongoing evaluation of medicines funded under the proposed Medicines for Rare Diseases Programme.

The reference group recognised the complexities of collecting evidence from small cohorts of patients with rare diseases, the lack of information on the natural histories of a rare disease, the multiple patient registers held by international companies and the different data collection initiatives available across the rare disease communities.

The reference group is of the view that a fit-for-purpose model should be developed with clarity as to the purpose of the data, what is required and how it might be used. It is important in doing this wherever possible to build on and incorporate already existing registries/databases. This will require existing custodians to be convinced of the value of joining such a database, and potentially resources to seek consent from patients to participate in the new database.

The reference group notes the work currently underway in Western Australia to develop such a database for Gaucher disease with the flexibility to be adapted to any rare disease. We also note that there may be scope within the redesigning of the national personal electronic health record (MyHealthRecord) for a consent-based linked data approach.

Recognising the financial burden that could be incurred by any single entity, the reference group proposed that the Department explore the funding of the data collection by the medicine sponsor as a component of a managed entry scheme for a rare disease drug. Funding may include remuneration for an administrative clerk or nurse at the clinic to enter data into an established registry.

10. The reference group considers some matters out of scope for the LSDP Review but recommends that further consideration be given to these matters raised by stakeholders.

Through the feedback and consultation the reference group became aware of a range of issues that fell outside its terms of reference but that it recognised as important for people with rare diseases, and for their families and carers, both now and in the future. These include:

- that the healthcare needs of people with rare diseases and their families identified in this review go beyond access to special medicines
- the need to facilitate consumer awareness about clinical trials of medicines for rare diseases.

The review also identified broader programme issues in access to medicines for rare diseases, including:

- the need for a more systematic and broader use of managed entry schemes for medicines for rare diseases
- the need for greater transparency in the cost of development and production of these medicines and their subsequent pricing
- the need to systematically review pricing of the medicines after recommendation, based on demonstration of effectiveness
- the need to examine ‘off-label’ use of PBS medicines to treat rare diseases.

The reference group recommends that these programme issues be considered further as part of the review of the guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee.

Section 4: Overview

4.1. Objective of the Life Saving Drugs Programme Post Market Review

The Life Saving Drugs Programme (LSDP) has provided essential treatments to Australians living with rare and life-threatening diseases since its inception through the Act of Grace payments in 1995 and later through the establishment of the LSDP proper. These rare disease medicines have very high cost per patient and consequently do not meet the comparative effectiveness and cost of therapy criteria required for PBS funding. The LSDP ensures eligible patients are able to access these life-saving medicines at no expense to the patients or their families.

4.2. The Life Saving Drugs Programme

In September 2015, the LSDP subsidised 10 medicines for eligible patients with one of seven rare and life threatening diseases at an average cost of over $311,000 per patient annually. In 2014–15, the programme treated 289 patients at a cost of approximately $85.9 million. Twelve additional patients were eligible to receive free access to life saving medicine treatments through the LSDP since the announcement of the LDSP Post Market Review in April 2014. In September 2015, the number of patients treated under the programme was 281.

4.3. Why are we reviewing the programme?

Like consumers, the Government wants to ensure that the health system delivers the highest standards of equity and quality in providing for individuals with rare diseases. The Government is equally concerned that subsidised medicines are effective and target the most severe diseases, whilst being mindful of the impacts and costs to patients and their families.

In the last few years there has been an increase in submissions for very highly priced medicines in line with increased interest in targeted therapies at the genomic level. Often these are targeted to small populations and seek inclusion to the LSDP. A review of the LSDP, in light of evolving scientific advancements and increased patient and industry expectations is important to ensure the programme remains viable and available to people who might need to access it in future.

4.4. What did we look at?

On 9 April 2014, the Minister for Health announced the LDSP Post Market Review. The main objectives were to review the access, equity, value for money and future administration of the programme with a view to facilitating continued subsidy to important and necessary medicines for patients in need, in an exciting but challenging environment of increasing demands for new and very highly priced therapies. The review also provided an opportunity to take stock of the clinical efficacy and safety data for treatments currently subsidised and to incorporate new or emerging evidence. In keeping with the objective of improving

processes and access for patients, the review looked at ways to improve data collection for rare diseases and to engage with stakeholders.

4.5. What was the process?

The process undertaken and stakeholder engagement during the review are summarised in Table 1 above.

In August 2013, the Department of Health asked the public for its views on the draft terms of reference for the LSDP review. Based on the feedback received, one of the terms of reference, which looked at assessing value for money of the medicines subsidised on the LSDP, was adjusted to include consideration of the 'quality of life' achieved through receiving treatment on the programme.

In March 2014 the Minister for Health approved the final terms of reference for the review. An independent reference group was established which drew from expertise in the fields of rare diseases, paediatrics, ethics, pharmacotherapy, public health and health economics and from consumer representations. The reference group met five times, including one teleconference, over the course of the review. The reference group also met with patients, patient organisations leaders and industry.

The Department commissioned an independent technical evaluation group, the University of Adelaide, to assess:

- the effectiveness and safety of medicines currently funded through the LSDP
- treatments and diseases for which funding through the LSDP may be sought in the future
- international approaches to defining rare diseases and funding medicines that treat those diseases
- the value for money of the currently funded drugs
- the establishment of a framework for collecting data on rare diseases in Australia and how this could function internationally.

The Consumers Health Forum of Australia (CHF), the national peak body representing the interests of Australian healthcare consumers, was contracted to consult patient and consumer groups on two of the terms of reference. The CHF's report is at **Appendix B**.

The Department sought public opinion in two further calls for public submissions. In August 2014, the public was asked to comment on the LSDP review terms of reference. Submissions were open for three months to enable all interested parties to contribute.

In April 2015, the reference group considered the draft technical assessment report from the University of Adelaide, and released an issues paper summarising issues they identified associated with the LSDP and rare diseases. The public and industry were invited to submit their views on the draft technical assessment report and the issues paper. The initial period of about three weeks of consultation was extended, first to those who requested an extension and later to all interested parties. In total, 58 submissions on the issues paper were received over five weeks.

4.6. Other consultations

Stakeholders met with members of the Department at a number of patient and consumer led events in Canberra, Melbourne and Sydney during the review. Two CHF-facilitated workshops were held in Sydney and Melbourne in March 2015. The reference group met with industry representatives in May 2015. A further telephone conference was held between the Chair and two members of the reference group and representatives of key patient/family disease interest organisations in May 2015.

4.7. Past review

In 2008, the Government reviewed the LSDP as part of the comprehensive expenditure review (CER) process. The purpose of this review was to establish consistent and rigorous procedures and a sustainable programme. The terms of reference specified that the review was to be conducted with due regard to the Government's CER principles of appropriateness, effectiveness, efficiency, performance assessment integration and strategic policy alignment.

That review was completed in January 2009. It resulted in revised funding criteria and conditions for the programme that became effective on 10 May 2010.

Three new medicines have been listed since the 2009 review:

- Soliris® (eculizumab), for the treatment of paroxysmal nocturnal haemoglobinuria, in 2010
- VPRIV® (velaglucerase), for the treatment of Gaucher disease (type 1), in 2012
- Myozyme® for the treatment of juvenile onset Pompe disease, in February 2015.

Section 5: Issues arising since the 2008–2009 Life Saving Drugs Programme review

A number of definitional issues were identified by stakeholders following the 2010 revised funding criteria. These definitional issues, described below, were also raised in submissions received from the public during the recent LSDP Post Market Review consultation processes.

Other dominant issues raised were the strong emphasis on 'survival or long-term survival' as a measure of value for money for patients receiving LSDP-subsidised medicines in both the Pharmaceutical Benefits Advisory Committee (PBAC) rule of rescue guidelines and the LSDP eligibility criteria.

As a consequence of these public comments, the terms of reference were expanded to include investigation of the definitional issues and to include quality of life in the evaluation of the benefit of treatment outcomes. The issues paper is at **Appendix A**.

5.1. Definitional issues

5.1.1 Criterion four: substantial

In 2010, criterion four was added to the criteria for listing new medicines under the LSDP. Criterion four required 'evidence acceptable to the Pharmaceutical Benefits Advisory Committee (PBAC) to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug'.

Stakeholders criticised this criterion as being subjective and ambiguous in that 'substantially' or 'substantial benefit' was not defined in the *National Health Act 1953* or in the PBAC guidelines. The lack of definition created uncertainty for industry and patients seeking reimbursement and access through the LSDP. Similarly, industry questioned what would constitute 'evidence acceptable' to the PBAC given the small patient populations and clinical trials typical of medicines for this cohort. Consumers, including patient organisations, have also criticised the criterion for focusing solely on a benefit in terms of survival and for not recognising the value of quality of life improvements.

In addition, the criterion also stated 'there is a rare but clinically definable disease for which the medicine is regarded as a proven therapeutic modality, i.e. approved for that indication by the TGA'. This was problematic in the absence of any definition of 'rare' within the Act and the fact that treatments for very small numbers of patients are routinely subsidised through the PBS.

5.1.2 Criterion five: clinically effective but rejected for PBS listing because it has failed to meet the required cost-effectiveness criteria

Criterion five requires the medicine to be rejected for listing on the PBS for failing to be cost-effective when compared to other alternative therapies, whether or not the alternatives involve the use of other medicines or preparations. This has created perverse

incentives for industry to price medicines such that the medicines are not considered cost-effective by the PBAC when compared to alternative treatments.

Criteria four and five have been used recently by a number of sponsors of medicines in Australia to target sub-sets of patients (such as a small number of cystic fibrosis or cancer patients with a specific genetic mutation) to argue that they should be funded in the LSDP rather than be considered under the usual PBS criterion of cost-effectiveness.

Criterion five has also led to manufacturers' interest in seeking orphan drug designation or 'rare disease' status for medicines for more common diseases which affect smaller subgroups within the population, to take advantage of orphan drug programme initiatives globally. This has generated an increasing number of very highly priced medicines for small populations and is a challenge for government, payers and medicine reimbursement authorities around the world.

On 29 May 2015, the *Wall Street Journal* reported that 50 per cent of acquisition deals among medicine manufacturers since August 2014 included an orphan drug. The *Wall Street Journal* also noted that EvaluatePharma, a market research firm, reported that global sales of orphan medicines are expected to rise 10.5 per cent annually to about $176 billion in 2020. This gives an indication of the attractiveness of orphan medicines or medicines for small populations to medicine developers and manufacturers (Pharmalot 2015 http://blogs.wsj.com/pharmalot/2015/05/29/heres-why-orphan-drugs-will-remain-attractive-ma-targets/).

5.1.3 Conflation of rare disease drug subsidy and orphan drugs

For a medicine to be successfully included in the LSDP, the medicine must also be approved by the TGA as a proven therapeutic modality for the specified 'rare but clinically definable disease'. However, as discussed above, the National Health Act, which sets out the roles and functions of the PBAC, does not define 'rare disease'.

Regulation 2 of the Therapeutic Goods Regulations 1990 define rare disease as 'a disease, or condition, likely to affect not more than 2,000 individuals in Australia at any time'. The reference to 'not more than 2,000' is also seen in Regulation 16I(4), which requires 'applications for vaccines or in vivo diagnostic agents requesting designation as an orphan drug' to state that 'the vaccine or agent will be administered in Australia to not more than 2,000 people in each year after it is registered for use for the disease or condition'.

The Regulations govern administration of the Orphan Drugs Programme, which has as its purpose to provide incentives to medicine sponsors to develop and bring to market medicines that affect small populations and would not otherwise be commercially viable. Regulation 16H specifies that, among other requirements, an orphan drug 'must be intended to treat, prevent or diagnose a rare disease' or 'must not be commercially viable to supply to treat, prevent or diagnose another disease or condition'. Regulation 45(12) provides a waiver of fees in relation to the designation, evaluation and registration of orphan drugs.

The objectives of the PBS and the LSDP differ from that of the Orphan Drugs Programme. The Orphan Drugs Programme gives medicine sponsors an exemption or relief from the TGA's cost-recovery mechanism. In doing so, it introduces an incentive for industry to research, develop and market the orphan drugs. The PBS and the LSDP are Government

reimbursement programmes which seek to subsidise the cost of medicines to the community on the evidence of comparative effectiveness and cost. Through these mechanisms, the PBS and the LSDP deliver health outcomes to the Australian public.

Consistent with the Government's policy of providing relief from cost recovery for a medicine that has been designated as an orphan drug, an orphan drug also attracts a waiver of fees for drug applications submitted to the PBAC for consideration of PBS funding.

5.1.4 Name of the programme

The name Life Saving Drugs Programme is unclear and does not reflect the objectives or the target population of the programme. Stakeholders have argued that medicines that treat chronic disease such as insulin for diabetes or chemotherapeutic medicines could be classified as life-saving.

5.1.5 No agreed definition of rare disease

There is no consistent definition of rare disease in comparable countries. In Australia rare disease is defined as a disease affecting fewer than 2,000 Australians or a prevalence of less than about 1 in 10,000. Table 4 provides examples of the different definitions used.

Table 4: Definition of rare disease in comparable countries

Region/organisation	Definition of 'rare disease'
Australia: Therapeutic Goods Administration (Australian Government 1990)	Affects ≤2,000 Australians, i.e. prevalence of about <1 in 10,000
Ontario, Canada (Ontario Public Drug Programs) (Canadian Agency for Drugs and Technologies in Health 2013)	Incidence rate of <1:150,000 live births or new diagnoses per year
Alberta, Canada: Alberta Human Services (Alberta Health and Wellness 2008; Canadian Agency for Drugs and Technologies in Health 2013)	Genetic lysosomal storage disorders occurring <1 in 50,000 Canadians
European Medicines Agency (Canadian Agency for Drugs and Technologies in Health 2013)	Prevalence of <5 in 10,000
Sweden: Swedish National Health Service (Visschers, van Gemert & Olde Damink 2011)	Prevalence of <1 in 10,000
United Kingdom: National Institute for Clinical Excellence (Picavet, Cassiman & Simoens 2013)	Affects <1000 people in England and Wales, i.e. prevalence of <1 in 50,000[a]
United States: Food and Drug Administration (Visschers, van Gemert & Olde Damink 2011)	Affects <200,000 Americans, i.e. prevalence of <1 in 1,500
Japan: Ministry of Health, Labour and Welfare (Gao, Song & Tang 2013)	Affects <50,000 people in Japan, i.e. prevalence of <4 in 10,000
South Korea: Ministry of Food and Drug Safety, formerly known as the Korean Food and Drug Administration (Gao, Song & Tang 2013)	Affects <20,000 people in Korea, i.e. prevalence of <4 in 10,000
China (Ma et al. 2011; Song et al. 2012)	Rare disease not clearly defined by legislation Consensus on the definition of rare disease: prevalence of <1 in 500,000 or neonatal incidence of <1 in 10,000

[a] Definition of ultra-rare disease.

Source: Table 137, Life Saving Drugs Programme Review: Technical Assessment, April 2015, p. 232.

5.2. Dissolution of the disease advisory committees in 2014

Prior to 1 May 2014, the Department of Health delegate relied on five disease advisory committees (DACs) to assess patient applications and make clinical recommendations regarding initial and continued eligibility for individuals to receive Government-subsidised treatment through the LSDP.

Each committee comprised a chair and four or five clinical experts in the relevant disease area. Some experts sat on multiple committees. As part of normal committee processes and transparency, the Department received conflict-of-interest declarations for all committee members, including DAC members.

Unsurprisingly given the small number of experts in this field, some DAC members declared dual advisory roles – that is, some members acted to advise the Government on the eligibility of patients receiving LSDP drugs while also acting in an advisory position for industry supplying the medicine to the Government. Other members of the DACs were also involved in clinically managing and caring for patients receiving treatment under the LSDP.

In March 2014, as part of the Government's deregulation agenda, the Minister for Health approved streamlining of the LSDP administrative processes at the same time when the post-market review of the LSDP was announced.

Streamlining reduced the administrative burden on all DAC members and allowed members to freely advocate on behalf of their patients, and to share their expertise with colleagues directly rather than through the DAC. It was considered that clinical experts would continue to share, network and improve their knowledge at conferences and other meetings.

Section 6: Life Saving Drugs Programme Reference Group paper April 2015

6.1. Life Saving Drugs Programme technical assessment report

The Adelaide Health Technology Assessment (AHTA), University of Adelaide (the evaluator) was contracted by the Government to examine the technical aspects of terms of reference 1, 2, 3, 5 and 7. The evaluator was asked to:

- look at whether there was new information on the safety and effectiveness of medicines currently funded through the LSDP and whether the information added support to the original funding recommendations
- scan for new and emerging technologies that might be relevant to the LSDP in the near future
- assess how medicines that treat rare disease are subsidised in other countries
- identify published literature reporting on cost-effectiveness and quality-of-life measures or other metrics for determining 'value' or identify alternative potentially useful metrics to measure 'value'
- provide a summary of key concepts related to data collection for rare diseases in Australia and methods for addressing the goals of such a data collection.

The evaluator undertook to develop a protocol to conduct systematic reviews of the evidence on all LSDP-subsidised medicines and analysed Australian data contained in the patient registries on the use of the drugs. The findings of the technical assessment (the evaluator's report) were presented to the reference group. The findings of the evaluator's report are summarised below.

6.1.2 Term of reference 1

Review the clinical effectiveness and safety of medicines currently subsidised through the LSDP.

- The evidence for Gaucher disease type 1 supported the funding of imiglucerase. The evidence on miglustat did not include any data on the treatment population proposed by the sponsor.
- No new evidence was found to change the conclusion on funding arrangements of treatments for Fabry disease, infantile-onset and juvenile onset Pompe disease and paroxysmal nocturnal haemoglobinuria.
  New data for mucopolysaccharidosis types I, II and VI is unlikely to change funding recommendations for these diseases.

6.1.3 Term of reference 2

Review emerging clinical treatments and diseases, including those that identify subgroups by molecular target, which could potentially seek subsidisation through the LSDP in the future.

- Emerging clinical treatments use a variety of mechanisms to treat severe diseases. Treatment types of growing importance are monoclonal antibodies and gene therapies. Some rare conditions are also being targeted with medicines that are already used for different clinical indications, and this could have implications for the public funding of these treatments.
- The increase in knowledge regarding causative genetic mutations responsible for many common conditions is now being divided into many different rare subtypes. These subtypes can be individually targeted with medicines that could be potentially eligible for the LSDP. It is possible that in the future, the majority of medicines being developed would fit this category.
- Given that the rarity of disease is one of the current criteria for eligibility for the LSDP, an increase in the number of medicines targeting this one criterion may increase the total number of medicines eligible for the LSDP.

6.1.4 Term of reference 3

Conduct an international comparison of subsidisation of drugs for rare diseases and the definitions for a rare/ultra-rare disease.

- Many funding bodies allow special consideration of orphan drugs, such as a relaxed requirement for pharmacoeconomic evaluation (Belgium, the Netherlands, Germany, Sweden and France), a higher cost-effectiveness threshold (Sweden), consideration of a broader societal perspective (UK), an acceptance of poorer quality evidence (Belgium, Sweden and France), or placement of greater weight in decision-making on the lack of alternative treatments (Germany, Italy and France).
- Pricing and funding decisions are monitored in Belgium, where medicine companies are expected to submit a revised medicine submission dossier 1.5 to 3 years following initial approval; in the Netherlands, where evidence is reappraised after 3 years; in France, where a listing is only valid for 5 years; and in the UK, where evidence is assessed after 5 years.
- Funding bodies apply different mechanisms to manage these high-cost medicines including managed entry schemes, performance-based risk sharing and financial-based schemes.
- In Australia, the LSDP does not require a reassessment of the funding decision on a listing following its initial approval, although this can occur on an ad hoc basis. Managed entry schemes and risk sharing are used as appropriate and with advice from the medicine sponsors.

6.1.5 Term of reference 5

Assess the value for money of the medicines subsidised on the LSDP by evaluating the benefit of each drug's treatment outcomes, including in terms of quality of life achieved through the programme, and their cost.

Other than routine cost–utility analyses, alternative approaches identified to evaluate the benefit of each of the LSDP drugs' treatment outcomes were:

- broadened cost–utility evaluation, with improved sensitivity and broadened perspective

- equity-weighted cost–utility evaluation, using various weighting criteria – e.g. disease severity (non-specific to orphan drugs), or rarity (specific to orphan drugs)
- multi-criteria decision analysis
- input-based costing.

The evaluator noted that conducting a 'value' assessment on existing medicines on the LSDP was difficult, irrespective of the metric used, because of the limited evidence available to measure the clinical effectiveness of the drugs.

6.1.6 Term of reference 7

Establish a framework for data collection on rare diseases in Australia and assess how this could function internationally.

The evaluator differentiated between rare disease registries and drug surveillance registries. The evaluator reported that, whilst drug surveillance registries are useful to collect data to address uncertainties regarding claims of the efficacy and safety of orphan medicines for the cohort of patients receiving treatment with the drug(s), the key purposes of rare disease registries are to (i) connect affected patients, families and clinicians; (ii) study the natural history of a disease; (iii) support research; and (iv) establish a patient base for evaluating drugs.

It was important to design each of the registries in accordance with its purpose. The likely objectives of the proposed surveillance registry for medicines being reimbursed through the LSDP are to:

- verify initial and ongoing eligibility of patients receiving subsidised medicines against the initially determined eligibility criteria
- measure the costs of the medicine and management of the programme
- evaluate the safety and effectiveness of the medicine against the claims made in the submission for funding through the LSDP
- use cost, safety and effectiveness data to support outcome-based risk-share arrangements between sponsors and government
- ensure adequate data collection to meet the aims of the registry
- ensure access to the data by key stakeholders.

6.1.7 Conclusion

The technical report concluded that most of the medicines subsidised by the LSDP are clinically effective and have acceptable safety profiles. There are indications that the LSDP is likely to be unsustainable in the future given medicine development and marketing trends. International experience in the public funding of orphan medicines and from economic theory suggests that a range of approaches might be adopted to work towards a sustainable LSDP. A drug surveillance registry may help determine whether each medicine performs as expected.

6.2. Reference group consideration of evaluator's report

The reference group considered the findings of the evaluator's report against each of its terms of reference. It considered whether there was more recent evidence for each disease and medicine class, since the initial decision to include a medicine in the LSDP, to show that:

- the medications were effective or ineffective
- the clinical benefits were less than what was claimed when the medicine was originally evaluated for inclusion on the LSDP
- the risks or side-effects were greater than what was claimed when the medicine was originally evaluated
- there was therapeutic equivalence where there is more than one medication in the same class
- there was additional evidence on whether individuals were or were not responding to treatment.

The reference group concluded that long-term efficacy data had not increased substantially despite the medicines being on the market for many years. At the same time, there was no new evidence to suggest that the original recommendation to include the medicines on the LSDP should be amended. The reference group also noted that, while none of the LSDP medicines cured the disease, all showed an effect in slowing progression of the disease. In some instances, progression of the diseases was reversed.

The reference group suggests that treating physicians should be supported in decisions to cease treatment in situations where there is continued deterioration in the patient's condition despite continued administration of treatment and there is no substantial patient benefit. Reference to clear expert-endorsed stopping rules is paramount and all decisions should be in consultation with the patient, carers and clinical experts.

The reference group published an issues paper in April 2015 summarising its considerations of the technical report and its initial views on each of the terms of reference. Public opinion (including relevant clinical groups, patient advocacy groups and medicine companies) on the 10 main issues was sought. A summary of the stakeholders' views in relation to each of the issue is presented below.

6.3. Summary of public comments on issues paper

6.3.1 Issue 1

The LSDP provides access to medicines but this is usually before there is clear evidence that the medicine is effective in the medium and long term. Consequently, the manufacturer may be being paid for a medicine that is subsequently shown to be ineffective or less effective than originally claimed. Theoretically the medicine could be more effective than originally claimed.

Should the Government expect some further evidence to support a continued benefit for patients through mechanisms like managed entry schemes and pay-for-performance mechanisms when the relative effectiveness of a medicine is not clear?

- Should the Government expect that sponsor companies share the uncertainty of the benefit through risk-share arrangements or similar mechanisms?
- What criteria should the Government use in determining what is a reasonable cost to pay for such drugs?

There is evidence through data that is being collected to show that medicines on the LSDP are effective. Enzyme replacement therapy has reduced the severity of symptoms associated with rare diseases.

Stakeholders generally supported the need for sponsor companies to provide further evidence to government and evaluating authorities for continued public funding of the LSDP medicines and to demonstrate the benefit of the drug. Government should expect sponsor companies to share the uncertainty of the health benefits through risk-share arrangements or similar mechanisms, as long as there is still incentive for companies to keep investing in much-needed rare disease research. Most importantly patients should be able to have timely and equitable access to treatment.

Many agreed that costs should be managed and negotiated by government and the medicine sponsors. One submission suggested cost per quality-adjusted life year (QALY) should be provided. A managed entry scheme (MES) coupled with risk-share arrangements may be useful to fast-track a medicine where there is no alternative effective treatment. Clinicians must have accepted the medicine as being efficacious. Sponsors, however, should not expect an automatic rise in prices with the provision of additional data. Patients receiving medicines under the MES must be made aware that evaluation of the medicine is ongoing and there could be risks that the medicine is toxic or ineffective.

Stakeholders believe that there should be explicit and pre-agreed criteria for determining reasonable cost of a drug. This should not be tied to continued funding of the drug. Reasonable cost should cover costs plus reasonable profit.

One submission suggested using a model proposed by Luzzatto et al (2015) to negotiate the cost of the orphan medicines systematically based on the documented cost incurred during the development of an orphan drug, an estimated number of eligible patients, and allowance for a reasonable margin of profit. Recognising the common interest in other countries grappling with rising healthcare costs and the cost of these drugs, and the size of the Australian market, the submission suggested that national governmental medicine agencies and insurance agencies should combine to negotiate with the pharmaceutical companies. Another proposal offered was for government to partner with companies to define research priorities in rare diseases and product development to avoid sponsors expending resources without certainty of recouping costs. Tendering was also touted as an option.

6.3.2 Issue 2

The reference group concluded that none of the medicines subsidised through the LSDP have been shown to cure the disease for which they are subsidised. With all of the medicines, progression of the disease may be slowed, though not reversed. Experience with the medications has identified patients where there is a continued deterioration in the patient's condition despite the continued administration of the relevant medication.

The review of evidence and published literature shows that some patients continue to deteriorate despite receiving continued relevant medication.

Is it reasonable to continue therapy when the patient's disease progressively deteriorates as assessed by clinical parameters and clinical assessments?

- Who should decide to continue therapy if the disease and/or the disease symptoms are not stable or improving (i.e. the disease is progressing)?
- Under what circumstances would a patient or clinician consider that the person has a benefit even when their disease is progressing?

Responses noted that there is no cure for most rare diseases such as those included on the LSDP. However, stabilisation of the condition, slowing disease progression and improved quality of life are valuable outcomes. Contrary to the statement in the issues paper, responses argued that there is clinical evidence that enzyme replacement therapy reverses progression. This statement was concluded in view of the evidence provided in the evaluator's report where evidence was reviewed in accordance with accepted scientific practices (the National Health Medical Research Council Evidence Hierarchy for Interventional Evidence (Merlin, Weston & Tooher 2009)). However, this meant that evidence of a lesser level was not considered if evidence of a higher standard was available. This distorted the evidence presented.

Submissions were divided on the continuation of therapy in the face of continued deterioration. Some submissions suggested that if a patient continues to deteriorate despite therapy then withdrawal of therapy is reasonable provided there is continued monitoring and symptomatic management. If the deterioration rate accelerates beyond expected rates, there should be a mechanism to reinstate therapy.

Withdrawal of treatments must be within pre-defined parameters and deliberations must be transparent. Others suggested that therapy should continue as deterioration could be temporary and due to unknown factors. Another suggested deriving a cost per QALY and building it into the drug authority restrictions as an aid when deciding whether to cease treatment. All agreed that the treating specialist in consultation with the patient/carer should make the decision. One submission noted that pre-agreed criteria may not be possible for all cases, and recommended oversight by a panel of experts.

6.3.3 Issue 3

Clinicians and patients currently agree to certain conditions, including discontinuation of the LSDP subsidy if the patient ceases to benefit from administration of the drug, prior to the approval of the funding.

- Should such decisions be binding on all decision makers – i.e. the prescriber, the consumer and the Government? If not, why not?

Responses indicated that the Government has a responsibility to listen to patients and protect them. Some submissions stated that all parties should abide by the legally binding agreement on the initiating and discontinuing conditions entered into at the start of the treatment. Any decision to enforce withdrawal should be undertaken with guidance from local or international clinical experts and exercised with caution as it may cause irreparable damage. One submission only supported withdrawing treatment if the medicine was not well tolerated or if there were serious adverse effects.

6.3.4 Issue 4

Many medicines subsidised on the Pharmaceutical Benefits Scheme (PBS) could be considered to be life-saving. In contrast the extent to which some of the LSDP listed

medicines are life-saving is questionable. Many new therapies are emerging on the market. These new medicines may treat the rarer subgroups of more common diseases.

- Some of the new treatments emerging for genetically inherited diseases such as those currently treated on the LSDP will not be medicines in the conventional sense. Some may be tailored to the specific genetic subtypes of each individual for a more common disease.
- Should the LSDP be extended to treatments that are specific to one or two individuals and/or to small subsets of individuals with a unique rare mutation which responds to a specific therapy (i.e. truly individualised therapy)?
- If so are the criteria of value and effectiveness currently used by the Pharmaceutical Benefits Advisory Committee (PBAC) still relevant? If not what should be the criteria for each of the groups referred to in the question above?
- Should there be a distinction between the types of diseases with treatments on the LSDP for rarer subtypes of more common diseases and rare diseases?

Responses noted that, in general, society has not discussed putting a cap on the total amount spent per patient and that a patient would expect to receive optimised therapy specific to the patient need. It was also commented that, as long as a high-cost medicine offers a significant health benefit, there is no moral difference between providing high-cost medicines for small groups of patients with rare genetic diseases and those with genetic subgroups of common diseases. A common process involving the evaluation of safety, effectiveness and efficiency of the medicine should apply with some variation in the level of evidence provided when assessing funding. One submission stated that it was not equitable to have no limits on cost-effectiveness based on rarity alone. Many other submissions contended that the LSDP, or any iteration of it, should remain true to its original objective, which was to provide subsidies to people with rare diseases or very rare diseases only.

6.3.5 Issue 5

There are a number of definitions for rare diseases. The defined prevalence ranges from 1 in 1,500 to 1 in 500,000. Regulation 2 of the Therapeutic Goods Regulations 1990 defines rare disease as a disease or condition likely to affect not more than 2,000 individuals in Australia at any time, representing a prevalence at the time of 1 in 10,000. The definition of rare disease varies between countries and agencies. There are also other factors that may be relevant such as the impact of the disease and the availability of existing treatments.

- Should there be an explicit definition of what constitutes a rare disease for purposes of public funding and, if so, what should that be?
- What criteria other than effectiveness should be taken into account in deciding the merits of public subsidy for a new medicine under this category?
- What mechanism should be used to measure those criteria in a valid and reproducible way that could be applied generally to other medicines seeking subsidy for rare diseases?

Responses to this issue indicated that a definition of what is rare would assist with identifying the level of evidence required for subsidising the medicine. The Therapeutic Goods Regulations' definition of rare as a prevalence of less than 1 in 10, 000 was accepted as suitable by clinical practitioners. One submission raised questions about how disease should be defined – should it be specified by a specific gene mutation or specific enzyme

level, or by severity, and how should the severity of a disease be defined (e.g. MPS I spectrum of Hurler, Hurler-Scheie and Scheie syndromes)? Another submission suggested that an expert panel with relevant expertise in the disease and a patient care ethicist should be appointed to assist not only in providing guidance to these questions but also to advise on decisions about continued funding of the medicines in patients, disease criteria, guidelines and health outcomes for funding purposes.

The definition requires broader consultation and there should be clarity and transparency about the criteria used for any new definition. Several submissions proposed adopting a definition consistent with the European definition of no more than 5 in 10,000 whilst others believed the current prevalence of 1 in 10,000 is reasonable. The proposed definition of rarity in the issues paper would affect many across the rare disease population in Australia and the implications must be fully understood.

The Rare Voices Australia definition of rare disease – 'any disorder or condition that is a life-threatening or chronically debilitating disease which is statistically rare, with an estimated prevalence of 5 in 10,000 or of similarly low prevalence and high level of complexity that special combined efforts are needed to address the disorder or condition' was suggested by a number of submissions.

6.3.6 Issue 6

The PBAC is required by law to consider the cost-effectiveness of any new medication. The PBAC also takes into account other factors such as the affordability if not subsidised, availability of other effective therapies, severity of the medical condition, equity, unmet need and special need situations such as children and Indigenous populations. 'Rule of rescue' is applied when the medicine is presented as an agent of last resort. Rule of rescue has four main considerations: (i) no alternative treatment is available in Australia, (ii) the condition is severe, progressive and expected to lead to premature death, (iii) there is a small number of patients who would be treated, and (iv) a worthwhile clinical improvement is achieved.

For further information on the rule of rescue refer to http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html*.*

There currently exists a number of separate programmes that fund high-cost and specific therapy medicines, including the LSDP and medicines approved by the PBAC under the rule of rescue and section 100 highly specialised drugs.

- Should the LSDP be continued as a separate programme? If so, why?
- Should there be one overarching subsidisation programme that applies to all high-cost and/or specialised medicines (including those on the LSDP and those available through the PBS section 100 highly specialised drugs)?
- What criteria would be applied to such a programme that would distinguish them from other medicines subsidised on the PBS, for relatively common conditions?
- Should a programme that subsidises high-cost and/or specialised medicines have one set of decision rules that apply to all medicines meeting those criteria?
- Should there be one set of criteria to cover both high-cost and specialised drugs?

Most submissions supported keeping the LSDP as a separate programme but accepted that it may be integrated within an existing administrative structure such as the section 100 Highly Specialised Drugs Programme (HSDP). It is contended that the best use of funds will

only be achieved if appropriate patients are identified and there is continuous monitoring of and research on patients treated with the subsidised drugs.

Benchmarking against similar systems was encouraged. A few submissions believed that the LSDP should be incorporated into an overarching programme for medicines. One submission proposed that ethical principles for allocating resources should be applied and that this may be achieved more easily if similar programmes like the LSDP, the HSDP and the PBAC rule of rescue were consolidated. This comes with the recognition that criteria for rare diseases would address the economic barriers faced in treating small populations and assessments must recognise decisions that may be applicable to the broader populations versus ones that apply at the individual level. Assessment of benefits should include quality of life.

The rule of rescue is appropriate for the majority of the medicines subsidised by the LSDP but some modifications are necessary to broaden the factors considered. Factors which could be considered to broaden the assessment of LSDP-type medicines for subsidy can include, as appropriate, quality of life and combination therapies, particularly where an expensive drug may be used for a short period of time in conjunction with another therapy. An example of the latter is in cases of MPS I Hurler syndrome where idursulphase may be used for a defined period prior to and after stem cell transplant.

6.3.7 Issue 7

There is inadequate evidence to address the value for money of medicines subsidised under the LSDP.

Clinicians could be encouraged to fill this gap by conducting research and providing evidence of dosing by body weight, where there is more than one medical agent in the same medicinal class, provide information of therapeutic equivalence, frequency of administration of treatment and provide information and clarification of when patients are not responding to treatment.

- What incentives are required to encourage clinicians and/or companies to undertake this type of research?
- To what extent should continuance of public money for the purposes of subsidy be linked to companies and/or clinicians undertaking such research?

Submissions noted that responsible stewardship of taxpayers' money requires post-market drug surveillance and regular mandated reviews. The initial decision to subsidise a medicine does not imply ongoing subsidisation. Sponsors should be responsible for ongoing research and monitoring of patients for medicines funded through the managed entry scheme. While desirable, research by clinicians is difficult as they are stretched for time and resources.

Some submissions considered a national database hosting data of all patients within each disease group, not only those who are subsidised, to be important. One submission suggested an international database coordinated by the World Health Organization as ideal.

Some comments noted that the post-market review of the LSDP has focused on costs to the federal health budget and is lacking in its consideration of the overall cost of managing the diseases for the family, the state and the general population. It was noted that not treating patients could cost more as demands on the health system increase as the condition of the patient regresses. Other comments noted that rare diseases require a fit-for-purpose

approach and that safe and effective treatments approved by the TGA need to be accompanied by positive recommendations by the PBAC.

A specific recommendation was that the criteria for Fabry disease should be reviewed to ensure access to treatment for females and children. There should not be a difference in criteria between males and females.

There was no consensus among submissions about the Australian Treatment Guidelines. Some submissions proposed that a review be conducted to ensure that the guidelines are consistent with international best practice. Others believe that the current Australian Treatment Guidelines provide sufficient flexibility to accommodate variation in treatment and to manage small patient groups. There was agreement that treatment guidelines should be clear on the success and failure of the treatment, and should outline when a treatment should commence, continue and cease.

6.3.8 Issue 8

The access to and administration of medicines subsidised under the LSDP is managed by the Commonwealth Government but point of patient care is usually in public hospitals in the states and territories. Access to medicines for patients should be efficient and support good health care.

- Would establishing a small number of state-based centres of for rare disease expertise be more effective in delivering the best overall care? What are the benefits for patients, their carers and clinical services?
- Would patients and their carers be disadvantaged by this arrangement? How could this be overcome?
- Is there a better way to improve clinical management of these patients, other than these state-based centres?

One submission stated that if the LSDP were consolidated into a section 100 type programme, there would be no need for state based centres of rare disease expertise (CoEs). Another submission contended that new CoEs were unnecessary and would not provide specialist care given the small number of patients and lack of expertise as state-based paediatric hospitals already function in this capacity. Another concern was that state-based CoEs run the risk of diluting expertise. In contrast, there is a belief that centres with experience in dealing with rare disease would improve patient care and consequently patient health outcomes. It was noted that in reality CoEs are the only places where patients can access disease-specific multidisciplinary care. Such facilities should be able to test all major organs.

It was further commented that if CoEs are established, funding policies and management of the medicines must be managed centrally to mitigate against inequitable access due to geographic locations and 'postcode lottery'. It was the view of one submission that the states and territories would place less priority on providing funds to manage patients with rare diseases in the absence of a national policy or strategy on it.

6.3.9 Issue 9

The PBS is a well-established framework that delivers appropriate medicine subsidies to Australians. It has been in operation for over 60 years and has evolved from supplying

medicines in the British Pharmacopeia *to pensioners in 1948 to subsidising over 5,100 medicines in 2014.*

Under the PBS the Commonwealth subsidises many high-cost medicines that can only be supplied from hospitals to outpatients. These arrangements are known as Highly Specialised Medicines Programme or section 100 drugs, after the relevant part of the National Health Act 1953*. Section 100 allows alternative arrangements to be established where these are considered more appropriate. Other current section 100 programmes include Efficient Funding of Chemotherapy and the Growth Hormone Programme.*

One proposal under consideration is that, instead of having a separate programme for rare diseases, a special section 100 arrangement could be established that takes into account the rarity of the patients' condition. A set of criteria would need to be established for each rare disease, and the administration of the programme would be modelled on existing programmes like the Growth Hormone Programme.

- What are the advantages of establishing a section 100 special arrangement for rare conditions as opposed to having a separate LSDP? What are the disadvantages?
- Are there other approaches to access and medicine delivery than via a special PBS programme that should be considered?

A majority of submissions supported developing a new section 100 'Rare or Very Rare Disease Programme' or 'Special-Access Medicines for Inherited Rare Diseases Programme. A separate section 100 programme mirroring an established and successful delivery framework dedicated to rare diseases would minimise confusion. It has the potential to reduce administrative burden and deliver more certainty to clinicians, freeing them to care for their patients. Others called for a similar programme but suggested calling it 'Section 200 Rare Disease or Very Rare Disease Programme'.

A few submissions noted that the primary objective of the programme is for patients to have timely access to needed medicines. The system should be flexible to enable doses to be adjusted as necessary for individual needs but it should also be stringent enough to restrict the medicines to appropriately defined groups of patients. Any new framework or model would need to be clear about who is responsible for prescribing, funding and maintaining expertise within accredited centres. Rare disease treatment entails close monitoring and individualised patient treatment. Therefore automating the application process may risk inappropriate therapy.

Submissions suggested that a clinical expert committee with membership flexibility to draw on expertise depending on the medication and diseases being considered is important to provide advice in instances where standard protocols may not apply or where cases are borderline. Members of this clinical committee must have relevant experience and be represented by specialists from both paediatric and adult medicine backgrounds.

6.3.10 Issue 10

There is universal acknowledgement of the need for systematic collection of data and better data management in order to inform questions such as efficiency and ongoing benefit of subsidisation to patients and the Government. Many companies host their own patient registries. Additionally there are initiatives at the international level for rare disease data

collection but these do not produce suitable information required to evaluate the medicines for the purposes of subsidy.

Establishing or adapting a data registry and maintaining the registry is expensive and consideration should be given to improving the data collected and ensuring that the data collected is 'fit for purpose'.

- Should the cost of maintaining a data registry be distributed across all the stakeholders (government, medicine companies and patients)? How might this be done?
- Medicine companies often maintain their rare disease registries in order to provide regulatory agencies with additional clinical data, generally on safety (pharmaco-vigilance) and sometimes on the effectiveness of the medicine in the 'real world' setting. This data is not always adequate or fit for purpose to answer questions raised about longer term patient benefits. Should the companies marketing these medicines be responsible for collection and maintenance of data that is fit for purpose?
- If it is not done by the company that markets the drug, what other effective and cost-efficient approaches are there for establishing and maintaining data registries?

Submissions were mixed about who should be responsible for data collection and maintaining the registries. Nurses are usually responsible for collecting the data. It would be unrealistic to expect existing clinical staff to fund or resource this activity as there are only a small pool of clinicians with expertise in metabolic conditions in Australia and all are already fully involved in research, clinical trials or research reviews.

There was a consensus from a Consumers Health Forum of Australia (CHF) workshop that any registry (or registries) should be able to work in an international environment, but it would be important to agree on standards for ensuring the accuracy and consistency of the registry. An internationally linked registry would permit researchers to draw on overseas evidence in assessing the efficacy of treatments or the emergence of new medicines that could be considered for use in Australia. Similarly, information sharing between drug development companies would benefit patients and could facilitate earlier access to the medicines.

Many submissions agreed that the management of data could be improved through adequate funding, as most of this activity is unfunded. Responsibility for data collection and the registries should be shared between medicine companies and the Australian Government. Others felt more comfortable with state-sponsored registries since company-hosted data is at risk of conflicts of interest and may be used for profit gain. Companies should help fund the cost of maintaining any data collection system through imposing a levy on pharmaceutical companies or through the negotiated managed entry schemes. An independent registry, funded by the Department of Health, was also suggested. This option relies on healthcare providers to enter data and for the Department to provide incentives for the healthcare professionals to do so. Another proposal suggested enabling patients to enter their own data and having an independent body oversee the management of the registry.

It was suggested that management of rare disease registries could be modelled on current state-based cancer registries. There were suggestions that companies should be responsible

for collecting and maintaining data with the Government being responsible for scrutinising the data and charged with protecting the interests of patients and the public. A couple of submissions suggested developing an independent data registry for all rare diseases to collect information on the natural history of the disease. This independent data registry would cover all patients with rare diseases, including those who are not currently being treated.

It was reported that Genzyme currently maintains registries for Fabry, Gaucher, Pompe and MPS I disease which are open to all treated and untreated patients.

Stakeholders agreed that the focus and purpose of data collection must be clear and transparent with safeguards to protect the privacy of patients.

6.4. Medicine industry's proposal

Fourteen industry representatives representing eight pharmaceutical companies with interests in rare diseases met with the LSDP Reference Group in May 2015. The representatives proposed a two-step process for evaluating medicine submissions for rare disease and criteria for assessing rare disease. This process comprised an initial assessment of a drug's eligibility to be declared as a rare disease therapy, followed by a multi-stakeholder conversation prior to formal submission to the PBAC about (but not limited to) the:

- collection of appropriate data
- indication to be treated
- population to be treated
- conditions and criteria for commencing and stopping treatment
- management of the high cost of the drug
- possible risk sharing between the Government and industry.

The proposal was suggested as a way to 'ring-fence' medicines for rare diseases to reduce the risk of industry's propensity to 'slice an indication to maximise price', a situation that is currently encountered by regulatory and reimbursement authorities (see also TGA Orphan Drugs review discussion paper, January 2015).

The first step of the process is based on a set of proposed conditions that also seek to address common issues encountered by industry and health technology players when evaluating rare disease therapies. As articulated by industry, issues encountered are:

- a lower level evidence base because of a lack of long-term outcomes, use of surrogate end-points, heterogeneity in disease characteristics and medical history, challenges with sample size and statistical power, and ethical considerations which prohibit randomised and long-term studies
- a reliance on clinical opinion: clinical opinion is used to supplement evidence but there is a limited pool of treating clinicians
- challenges demonstrating value for money through cost-effectiveness due to the high cost of the drug, lack of survival data and lack of adequate cost offsets.

On 10 June 2015, industry tabled revised medicine entry criteria for its proposed 'Section 200 Very Rare Disease Programme'. The revised criteria proposed were that there must be a

high unmet clinical need based on an assessment of the prevalence and severity of the disease, including:

- the disease prevalence must be no more than 1 in 50,000 people
- the disease is a chronic degenerative disease that causes a substantial reduction in age-specific life expectancy or quality of life
- once the population treated by the drug exceeds a cumulative patient population of greater than 1 in 50,000 people per year a review of the therapy listing(s) will be conducted.

Further, the availability of an alternative medicine listed in section 200 does not disqualify the proposed medicine from consideration for the section 200 programme.

Once the medicine is accepted as a treatment for rare disease, the medicine submission is considered for reimbursement purposes. Under the National Health Act, the PBAC must consider the clinical effectiveness, comparative cost-effectiveness and cost of the medicine seeking listing on the PBS. The PBAC also considers the availability of other effective therapies, severity of the medical condition, equity, unmet clinical need and special need situations such as medicines for children or Indigenous populations.

The PBAC is commonly criticised for its perceived emphasis on cost-effectiveness. Industry claims that cost-effectiveness ensures maximum gains for each dollar spent but the value of quality of life is not given enough weight in the decision-making process. Other aspects of 'value' like treatment options, patients' and carer's contribution to the community, convenience and the carer's quality of life are also not given sufficient weight when assessing a medicine for inclusion on the LSDP or PBS. Multiple stakeholders have proposed that the PBAC broaden its view and assessment of 'value'. A popular proposal is to include a UK-style multi-criteria decision analysis to expand value assessment.

6.5. International perspectives on funding medicines for rare disease

The reimbursement of medicines to treat rare diseases presents a unique challenge to governments worldwide. Many countries have implemented orphan medicine frameworks to encourage research and development in this sector. Such paradigms reflect an understanding that management of treatment of rare diseases are different to the management and treatment of other diseases. In the current health treatment context, lack of existing treatment options and hence consideration of effectiveness, equity of access to experienced treatment centres, providing fair return on investments to the medicine companies, the high cost of medicines and increasing fiscal constraints represent some of the challenges faced by organisations and health technology assessment and reimbursement authorities.

LSDP Post Market Review term of reference three looked at how other countries are managing the costs of these expensive therapies. Unlike Australia, the Netherlands, Italy, England, Wales, and Ontario (Canada) have separate evaluation and funding mechanisms specific to orphan drugs. Alberta's rare drug programme is restricted to lysosomal storage disorders and is similar to the LSDP, i.e. disease prevalence of 1 in 50,000. Patients treated under the Alberta programme must consent to a number of conditions including:

- conditional initial and continued coverage are dependent upon clinical outcomes
- ongoing clinical outcome monitoring is mandatory
- inadequate patient response or deterioration, as defined by pre-established withdrawal criteria for a specific medicine and/or as assessed by the programme's clinical review panel, will dictate coverage discontinuation.

Note that the presence of a significant illness likely to affect life expectancy, outside of the rare disease itself, is considered a contraindication to medicine funding.

Belgium, the Netherlands and Germany reportedly require no pharmacoeconomic evaluation but do not preclude risk-sharing arrangements (Denis et al. 2011; Garau & Mestre-Ferrandiz 2009; Vegter et al. 2010). In Germany, the Pharmaceutical Market Reorganisation Act (AMNOG) requires all medicines seeking reimbursement to be subjected to an additional benefit analysis prior to listing for reimbursement by the Federal Joint Committee (GBA). A simplified process was implemented for new products with orphan drug status, where the manufacturer need only submit an extract of the dossier. The GBA will decide on the level of additional benefit as a drug with an orphan drug designation implies that there is additional benefit. This simplified process is restricted to orphan medicines with anticipated peak sales of €50 million per year. If the threshold is exceeded after the GBA's decision, a complete dossier has to be submitted by the manufacturer. At its core, the benefit dossier must present evidence of the drug's additional benefit over the appropriate comparator, defined as the clinically appropriate standard of care in the indication (Tordup et al. 2014).

Funding for rare diseases is re-evaluated after 1.5 to 5 years in Belgium, the Netherlands and the UK (Denis et al. 2011; Garau & Mestre-Ferrandiz 2009; Vegter et al. 2010).

Sweden applies different cost-effectiveness thresholds for different characteristics of disease-linked severity and accepts a lower level of evidence for orphan medicines (Denis et al. 2011; Garau & Mestre-Ferrandiz 2009). The Pharmaceutical Management Agency (PHARMAC) in New Zealand uses a clinical effectiveness and cost-effectiveness framework with additional consideration of societal factors to determine public reimbursement of drugs. In June 2014, PHARMAC established a contestable fund aimed at improving access to medicines for rare disorders. 'Rare' was defined as an identifiable and measurable patient population with a prevalence of 1 in 50,000 or less. Pharmaceutical companies were invited to bid for funding worth up to $25 million over five years. Medicines funded under this process will be listed on the Pharmaceutical Schedule.

In France, the clinical evidence required for orphan medicines is limited to phase 2 trials and literature reviews, reflecting the limitations of gathering evidence on rare conditions (Garau et al. 2009).

Morel et al. (2013) reviewed managed entry schemes for orphan medicines in Europe and found evidence of 42 managed entry schemes specific to 26 medicines implemented between 2006 and 2012 in five European countries (Belgium: n = 4; England and Wales: n = 8; Italy: n = 15; the Netherlands: n = 10; and Sweden: n = 5). The review found that performance-based risk-sharing arrangements (55 per cent; n = 23) were slightly more prevalent than financial-based schemes (n = 19) and that performance-based risk-sharing arrangements were relatively more common in Italy, the Netherlands and Sweden.

Financial-based schemes were mainly found in Belgium, England and Wales, and Italy. A summary of managed entry schemes is given in Table 5.

A review of reports and ongoing inquiries from other countries suggests that Australia is not alone in grappling with managing the growing cost of medicines to treat rare diseases or diseases that affect a small population.

Table 5: Overview of managed entry arrangements identified across five European countries, described by country and design

Types of MEAs	Country					Number of MEAs
	B	E	I	NL	S	
Performance-based arrangements						23
Performance-linked reimbursement schemes						
Money-back guarantees			x			8
Coverage with evidence development (CED)						
CED 'only with research'				x	x	15
Financial-based arrangements						19
Patient-level financial schemes						10
Discounted treatment initiation			x			6
Patient utilisation cap		x				2
Patient cost cap	x	x				2
Population-level financial schemes						9
Discount	x	x	x			7
Price-volume agreement with budget cap	x					2
Grand total	4	8	15	10	5	42

B = Belgium; E = England & Wales; I = Italy; NL= Netherlands; S = Sweden; CED = coverage with evidence development; MEA = managed entry arrangement.

Source: Morel et al 2013, cited on p. 237 of the evaluator's report, April 2015.

6.5.1 UK National Institute for Health and Care Excellence interim process and methods for assessing highly specialised technology

The reference group considered the evaluator's review of international approaches to the assessment and funding of medicines for rare disease. It noted that the UK National Institute for Health and Care Excellence (NICE) approach had similarities and differences to the Australian approach that deserved special consideration, particularly as it seemed to have relevance to many of the issues raised in submissions. Introduced in 2013, the NICE Highly Specialised Technologies Programme incorporates a 'simple' MCDA to assess public funding of ultra-rare diseases. The evaluation committee, comprising patient and carer organisations, academics, medicine sponsors and members from the National Health Service (NHS), advises the NHS Commissioning Board about the benefits and costs of the specialised technology (the drug) after considering each of the criteria listed below. The evaluation committee may recommend against the use of the technology if the benefits are found to be unproven or the costs of the technology are unreasonable.

The core criteria for the MCDA are:

- Nature of the condition
    - disease morbidity and patient clinical disability with current standard of care
    - impact of the disease on carer's quality of life
    - extent and nature of current treatment options
- Impact of the new technology
    - clinical effectiveness of the technology,
    - overall magnitude of health benefits to patients and, when relevant, carers
    - heterogeneity of health benefits within the population,
    - robustness of the current evidence and the contribution the guidance might make to strengthen it
    - treatment continuation rules
- Cost to the NHS and personal social services
    - budget impact in the NHS and personal social services
    - robustness of costing and budget impact information
    - patient access agreement
- Value for money
    - technical efficiency (the incremental benefit of the new technology compared to current treatment)
    - productive efficiency (the nature and extent of the other resources needed to enable the new technology to be used)
    - allocative efficiency (the impact of the new technology on the budget available for specialised commissioning)
- Impact of the technology beyond direct health benefits
    - whether there are significant benefits other than health
    - whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services
    - the potential for long-term benefits to the NHS of research and innovation
- Impact of the technology on the delivery of the specialised service
    - staffing and infrastructure requirements, including training and planning for expertise.

This MCDA tool is an interim method and will be reviewed through a public consultation process by NICE during 2015.

Similar to the PBAC, NICE's evaluation committee takes into account the nature and quality of evidence submitted by the medicine sponsor, critique of the medicine submission by independent academics, and clinical specialists', patients' and carers' perspectives when assessing the clinical effectiveness of a drug. As in the PBAC, the level of uncertainty between evidence presented and effectiveness in clinical practice, likely benefits delivered to different patient groups, potential health outcomes and side effects of the treatment on the patient compared to alternative treatments, if any, are weighed as well. The committee may consider alternative treatments, which may include therapies that do not have marketing authorisation for the indication but are accepted as part of established clinical practice for the indication.

6.6. Australian context

Currently Australia does not have a specific evaluation programme for medicines for rare diseases. Sponsors submit their product to the PBAC to evaluate clinical effectiveness and cost-effectiveness. Where applicable the rule of rescue applies; however, if the rare disease medicine fails to be listed on the PBS because it was deemed to be not cost-effective, it may be considered for inclusion on the LSDP. In Germany and France the review processes for medicines targeting rare diseases are also not separate from usual medicine subsidisation processes.

However, many drugs for the treatment of other rare diseases are funded under the general PBS process, including for cystic fibrosis and rare cancers. Specific subsidies are also provided for nutritional products for rare conditions.

In the Australian context, NICE's experience provides useful insight to issues that may reduce the stated outcomes and objectives of the MCDA. It is noteworthy that a full and transparent decision-making framework requires transparency and cooperation on the part of all stakeholders and this may not be easily achievable. Medicine companies are not always willing or able to publically disclose information on pricing arrangements or other information considered commercially sensitive.

Other issues in considering applying MCDA to assessing medicines for the LSDP or any new section 100/200 Medicines for Rare Diseases Programme include the inequity of applying the MCDA approach to decisions for rare disease medicines only. Wailoo, Tsuchiya & McCabe (2009) described that an integral aspect of any economic decision considers alternatives forgone (opportunity cost) and any additional identification of value in the assessed product, either through equity weights or increased valuation of certain criteria using an MCDA approach (evaluator's report, p. 252). Having different mechanisms to evaluate medicines using different valuation methods within the same public reimbursement authority could be inconsistent and controversial.

If a more complex MCDA is to be adopted (i.e. weighted multiple criteria through public or patient preferences), there will be a need to develop an agreed set of attribute weights. This could be difficult and would require consultations with diverse groups to obtain wide societal representation and agreement. The reference group was concerned that there are significant challenges in measuring broader benefits in a systematic and reproducible way. These could hinder rather than assist timely access to the drugs, increase regulatory and administrative burden and potentially drain stretched resources.

Irrespective of the metric used, there are significant limitations of the available evidence to measure the clinical effectiveness of existing medicines on the LSDP and other medicines for rare diseases in general. There are small numbers of patients with any one disease or condition. The disability and impacts on quality of life may be present from birth or may develop late and progress slowly over many years. Available medicines may only prevent or delay certain aspects of the disease. Further consideration is required to incorporate the level of uncertainty into any alternative value metric.

Table 6 shows a summary of benefits and disadvantages of different value metrics for orphan medicines prepared by the evaluators.

Table 6: Advantages and disadvantages of alternative value metrics for the assessment of orphan medicines for reimbursement decisions

Metric	Advantages	Disadvantages
Broadened cost–utility (CU) perspective	The ICER is a more accurate reflection of the complete value a medicine may offer to society. Relatively easy to incorporate into existing assessment process. Produces an objective, reproducible value metric.	Fails to reflect social preferences where allocation on an equity basis (i.e. non-utilitarian) is preferred. In practice, lack of data may limit the scope and accuracy of the economic model. Would generally increase the cost-effectiveness of many medicines but the magnitude of effect may rarely be decision altering.
Equity-weighted CU analysis (equity-adjusted QALYS or ICER threshold) Broad equity criteria 'Rarity' as a criterion	Once criteria are defined and weightings determined, then application to a conventional economic assessment (ICER) or an adjusted benchmark ICER is straightforward and easy to interpret. Weightings favour non-utilitarian social distribution preferences which are not apparent on conventional ICER calculations.	Selection criteria may be contentious. Arbitrarily allocated weightings are subjective and yet mathematically determined weightings are highly variable and would require further social research. Difficult to apply a weighting where the patient population is highly heterogeneous with respect to the weighting factor.
Multi-criteria decision analysis (MCDA)	Can potentially incorporate all identified social concerns and values associated with a medicine into a value metric. Can be set up with inclusion of fluid or contextual criteria (e.g. 'current priorities') allowing for change in health strategy or policy, without change in the process.	Selection criteria may be contentious. Although intended to be transparent, may become highly complex with reduced transparency. May have subjective components. Would require significant planning and set up to implement.
Value-based pricing based on cost	Objective determination of (input) value. Potentially provides incentive for research and investment in medicines for rare diseases with less financial risk to industry.	No consideration of 'output' value. Financial risk to funding body. Requires sensitive commercial operating cost information which is difficult to verify. No practical experience.
Combined methods (broad CU perspective / equity-adjusted CU / MCDA)	Likely to capture all aspects of a drug's potential value to society.	Risk of double-counting value elements. High level of complexity. Potentially reduced transparency.

Source: Table 141 of the evaluator's report, p. 250.

Section 7: Life Saving Drugs Programme Reference Group considerations

7.1. Definition of rare disease

The reference group noted there was substantial variation in how the terms rare disease, orphan disease and orphan medicines were used depending on the context. It noted and was sympathetic to the international movement to develop comprehensive national rare diseases programmes that provide for elements such as centres of diagnostic and treatment expertise, special support services to assist patients with rare disorders, and special research funding, in addition to access to medicines. The reference group acknowledged that at a practical level it needed to recommend a numeric definition of rare disease for the purposes of this program. It wanted to be clear that any definition it proposed needed to be seen as specific to the terms of reference of the review and the specific nature of the programme: that is, subsidy of medicines.

7.1.1 Potential implications if the definition of rare disease is expanded

The Therapeutic Goods Regulations 1990 define rare disease as 'a disease or condition likely to affect not more than 2,000 individuals in Australia at any one time'. This figure was on the basis of an incidence of 1 in 10,000, in a population of 20 million. The Therapeutic Goods Administration (TGA) Orphan Drugs Programme review discussion paper (TGA 2015) indicates that the TGA is considering an argument to adjust the patient threshold now that the Australian population has grown to 23.5 million.

During the LSDP public consultations, industry and patient advocacy groups have suggested aligning the definition of rare disease with that accepted by the European Medicines Agency and the UK National Institute for Health and Care Excellence: i.e. 'the disease must be life-threatening or chronically debilitating with a prevalence of fewer than 5 in 10,000'. One submission noted that if the definition proposed by the reference group in the issues paper were to be adopted there would be a 'profound effect for patients and communities and those people receiving treatments on the LSDP'. The submission goes on to say that 'in order for Australia to meet the needs of the rare disease community living with life limiting disease, the definition should be mindful of the definitions adopted in similar nations and give due consideration to the principles of fairness and equity for those living with a rare condition'. It concluded that the most logical definition for Australia to align with was the European Union (EU) definition.

Table 7 presents examples of diseases that would be described as a rare disease if the definition were changed to higher disease prevalence. The table also shows the Pharmaceutical Benefits Scheme (PBS) listed therapies for the diseases.

Table 7: Examples of diseases with a reported incidence or prevalence of 1 per 10,000 (10 per 100,000), 5 per 10,000 (50 per 100,000) and 1 per 50,000 (2–3 per 100,000)

Example diseases	Number of Australians with the disease	Example therapy for disease on PBS	Reported incidence or prevalence
Glial tumour[a]	Around 2,500[b]	Temozolomide, carmustine	1 per 10,000 (10 per 100,000)
Acute myeloid leukaemia	Around 1,400[c]	Azacitidine	1 per 10,000 (10 per 100,000)
Pancreatic cancer	Around 2,000[d]	Everolimus, sunitinib	1 per 10,000 (10 per 100,000)
Phenylketonuria	Approx. 1 in 10,000 births[e]	Amino acid formula with vitamins and minerals without phenylalanine	1 per 10,000 (10 per 100,000)
Cystic fibrosis	Around 3,500[f]	Dornase alfa, tobramycin, ivacaftor	5 per 10,000 (50 per 100,000)
Gastric cancer	Around 3,600[g]	Docetaxel, Fluorouracil	5 per 10,000 (50 per 100,000)
Malaria	Around 500[h]	Artemether with lumefantrine, atovaquone with proguanil	1 per 50,000 (2–3 per 100,000)
Mesothelioma	575[i]	Pemetrexed	1 per 50,000 (2–3 per 100,000)
Thalassemia	Around 500	Deferiprone	1 per 50,000 (2–3 per 100,000)

a Including astrocytomas, ependymal tumours, glioblastoma multiforme, and primitive neuroectodermal tumours.

b Source: Australian Institute of Health and Welfare 2012. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer Series no. 69. Cat. no. CAN 65. Canberra: AIHW. p. 43. Number of people living diagnosed with brain cancer, 5-year prevalence as at 2007.

c Source: Australian Institute of Health and Welfare 2012. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer Series no. 69. Cat. no. CAN 65. Canberra: AIHW. p. 31. Number of people living diagnosed with acute myeloid leukaemia, 5-year prevalence as at 2007.

d Source: Australian Institute of Health and Welfare 2012. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer Series no. 69. Cat. no. CAN 65. Canberra: AIHW. p. 111. Number of people living diagnosed with pancreatic cancer, 5-year prevalence as at 2007.

e Williams et al. (2008) Phenylketonuria: an Inborn error of phenylalanine metabolism. Clin Biochem Rev. 2008 Feb: 29(1): 31–41. In 2013 there were 308,065 registered births in Australia (ABS 3301.0 – Births, Australia, 2013).

f Based on 15th Annual Report Australian Cystic Fibrosis Data Registry.

g Source: Australian Institute of Health and Welfare 2012. Cancer survival and prevalence in Australia: period estimates from 1982 to 2010. Cancer Series no. 69. Cat. no. CAN 65. Canberra: AIHW. p. 119. Number of people living diagnosed with stomach cancer, 5-year prevalence as at 2007.

h National Arbovirus and Malaria Advisory Committee. 'Arboviral diseases and malaria in Australia, annual report 2011–12'. Based on 5-year mean cases.

i Australian Mesothelioma Registry '3rd Annual Report Mesothelioma in Australia 2013'. p. vi, number of newly diagnosed cases in the 2013 calendar year.

The reference group explored the implications of different definitions on numbers of patients potentially relevant to a Medicines for Rare Diseases Programme. For example, it noted that if the EU definition (5 in 10, 000) were adopted diseases such as gastric cancer

and cystic fibrosis would fall within the definition of 'rare'. Just these two additions to a programme would expand the potential patient population number fivefold – i.e. from the current 268 patients on the LSDP to up to 1,285 patients. If it were applied more broadly for all diseases then the maximum uptake of the 5 in 10,000 in a population of 23.5 million could be up to 11,700 patients. So while each disease/condition group would still meet the numeric definition of rare disease, a programme encompassing those diseases would not be what was originally envisaged in the LSDP.

As technology continues to advance, newer therapies will be developed for more rare diseases. The reference group was concerned that broadening the definition of rare disease would effectively change the original intent of the program, which clearly related to very rare diseases with a very high lifelong cost burden on individuals and their families. The reference group noted and was sympathetic to the broader concerns about access to medicines for less rare diseases. However, it was of the view that maintaining the stricter definition of rare disease was in the best interests of ensuring sustained government support for funding for medicines for very rare diseases with associated very high costs. It also sent a clear message to industry to encourage development of new medicines for very rare diseases.

The reference group noted comments that the impact of rare disease therapies is around 0.21 per cent of the total Commonwealth spend on healthcare in 2013–2014 and forecasted to be 0.24 per cent between 2013–2014 and 2017–2018. The reference group noted that this was on the basis of the current rate of subsidy and rare disease definition. The cumulative effects of extending the rare disease definition could have a significantly larger impact on the federal health budget. For example, if even the 1,285 patients identified above were treated under such scheme at the average current patient drug subsidy cost, the cost of the programme to taxpayers could increase from $77.5 million in 2014–2015 to $387.5 million. If the upper limit of 11,700 patients were to receive subsidy, the cost of the programme could be up to $3.5 billion. While cognisant that this is an extreme case, the reference group is concerned that the total cost of the programme would impact on continued Government support for a special program of funding for people with rare diseases.

It is noteworthy that stakeholders offered a number of approaches to reduce the costs of the rare disease programme. These include:

- having regular reviews of the drug's efficacy
- improving transparency on how companies priced their medicines
- examining how existing medicines listed on the PBS might be approved for 'off-label' use to treat rare diseases
- ensuring clear definitions both for rare disease and for the criteria for the programme.

7.2. Access to subsidised drugs

7.2.1 Continued access to Life Saving Drugs Programme funded drugs

Stakeholder submissions were focused on themes such as the ability of existing patients to access medicines currently listed on the LSDP, future administration of the LSDP, the effect

of a new delivery framework on existing patients, proposed criteria to assess new therapies for listing on the new LSDP administrative framework, and new patient access to the rare disease drugs.

For medicines already listed on the LSDP, the reference group recommended that, if a new delivery framework such as a section 100 rare disease treatment programme were adopted, regardless of how a medicine may be assessed in the future, existing patients should not be affected by the new assessment criteria for existing drugs. Treatment would be available to existing patients for the specific indication as long as the existing medicine is safe and continues to be manufactured for sale.

7.3. Section 100 as an option for a Medicines for Rare Diseases Programme

7.3.1 Section 100 special arrangements

Most medicines and medicinal preparations available to the public under the PBS are listed under section 85 of the *National Health Act 1953*. However, a smaller number of medicines are also distributed under alternative arrangements, as provided for in section 100 of the Act, where these are considered more appropriate.

Section 100 of the Act states:

(1) The Minister may make special arrangements for, or in relation to, providing that an adequate supply of pharmaceutical benefits will be available to persons:

… … …

(c) if the pharmaceutical benefits covered by the arrangements can be more conveniently or efficiently supplied under the arrangements.

… … …

(2) The Minister may vary or revoke a special arrangement made under subsection (1).

(3) This Part, and regulations or other instruments made for the purposes of this Part, have effect subject to a special arrangement made under subsection (1).

Note: For example, for a drug declared under subsection 85(2), it does not matter if a special arrangement for its supply is inconsistent with a determination made under subsection 85(3) or section 85A for the drug.

7.3.2 Section 100 special programmes

Many different programmes are already administered under this section. These include:

- Highly Specialised Drugs Programme
- Growth Hormone Programme
- Efficient Funding of Chemotherapy
- Botulinum Toxin Programme
- IVF/GIFT Programme
- Opiate Dependence Treatment Programme.

7.3.2. 1 Highly Specialised Drugs Programme

The Highly Specialised Drugs Programme is one example of the use of section 100. This programme subsidises medicines for the treatment of chronic conditions that, because of their clinical use or other special features, are restricted to supply through public and private hospitals that have access to appropriate specialist facilities. Medical practitioners may be required to be affiliated with these specialist hospital units in order to prescribe these medicines as PBS-funded items. A general practitioner or non-specialist hospital doctor may only prescribe highly specialised drugs to provide maintenance therapy under the guidance of the treating specialist.

PBS benefits are only available for the listed clinical indications and there is no facility for individual patient approval for indications outside those listed. For access to a medicine funded under this programme, a patient must meet a number of criteria. The criteria can include that the patient must:

- attend a participating hospital and be a day-admitted patient, a non-admitted patient or a patient on discharge
- be under appropriate specialist medical care
- meet the specific medical criteria
- be an Australian resident in Australia (or other eligible person).

The patient is required to pay a contribution for each supply of a highly specialised medicine at a similar rate to the PBS. Commonwealth subsidy is not available for hospital in-patients.

7.3.3 Section 100 Medicines for Rare Diseases Programme

The reference group considered the historical origins and objectives of the LSDP, set up through the Act of Grace by the Department of Finance and concluded that as it stands, there were no benefits and no extenuating reasons in retaining the LSDP as a standalone programme outside of the PBS. The reference group noted stakeholders' preference for the continuation of a special programme for funding rare diseases (summarised at section 6.3.9). It noted that there were mixed views about continuing the stand-alone programme or incorporating it under the PBS.

A number of programme names were suggested including Section 200 Rare and Very Rare Disease Therapies and Special Access Inherited Rare Disease Programme.

The reference group believed integrating the LSDP into a programme established under section 100 special arrangements of the *National Health Act 1953* was a reasonable and logical option. A new section 100 Medicines for Rare Diseases Programme would simplify and streamline administration of the subsidised rare disease medicines as the proposed programme will mirror elements of the section 100 Highly Specialised Drugs Programme and the Growth Hormone Programme. It considered that there was a strong case for all decisions about subsidies of medicines to be considered under a unified framework while acknowledging the need for special considerations for medicines for rare diseases. The reference group therefore recommended that the criteria for eligibility for inclusion to the new section 100 Medicines for Rare Diseases Programme should make allowances for issues

unique to reimbursing medicines for treatment of rare diseases such as the severity of the disease and rarity.

Appropriate multi-stakeholder consultations should be undertaken to further discuss the new framework and processes. Stakeholder input to the new framework if adopted, was favoured by patients, clinicians and industry submissions.

7.4 National Health Act and Pharmaceutical Benefits Advisory Committee role

The PBAC is established under the National Health Act. Its primary role is to recommend to the Minister for Health which medicines and medicinal preparations should be subsidised by the Australian Government under the PBS. In doing this, the PBAC is required by the Act to consider both the effectiveness and cost of the proposed medicines and medicinal preparations.

The PBAC Guidelines explains to sponsors and interested parties how to prepare a submission to list a new medicine or medicinal product on the PBS (i.e. for public funding). The guidelines provide instructions on the type of information required by the PBAC, and its Economic Sub-Committee (ESC), to support the proposed new medicine. It also instructs on the most appropriate form of clinical evidence and economic evaluation for specific submissions.

For some submissions, options to present additional relevant information in a submission are important. These factors may include equity principles, 'rule of rescue' and other factors that may influence the outcome of the submission. These factors are taken into account by the PBAC. Rare and ultra-rare diseases by their very nature have smaller patient cohorts. Smaller patient numbers in clinical trials will constrain data collection and affect the reliability and sufficiency of the data collected. The PBAC is aware of, and acknowledges the challenges faced by manufacturers of orphan medicines. However, while the PBAC itself does not set a minimum standard for the type and level of evidence or other information that can be included in a submission to PBAC, under the Act, the PBAC must consider comparative costs and effectiveness when assessing a medicine for listing on to the PBS. The Act does not state a value for when a medicine would be considered cost-effective.

Section 101(3A) of the Act states:

For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of medicines and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other medicines or preparations.

7.4.1 Factors influencing Pharmaceutical Benefits Advisory Group decision making

A report published in 2008 (Harris et al 2008) analysed all major medicine submissions to the PBAC, and the corresponding PBAC outcomes, for the period between February 1994 and December 2004. This equated to 858 submissions.

The study reported that clinical significance, cost-effectiveness, cost to government, and severity of disease were significant influences on PBAC decisions. Compared to the average submission, clinical significance increased the probability of recommending listing, by 21 percent. The probability of listing the medicine increased to 38 percent, in cases where the medicine was for life-threatening conditions. Analysis showed that the PBAC was substantially more likely to recommend subsidy in situations where the medicine treated diseases with a projected survival of less than five years. The availability of alternative treatments did not increase the likelihood of subsidy. The precision of the effect size estimate, the level of the evidence, and the quality of the studies did not have a significant effect on listing decisions for life-threatening conditions, though relevance of the evidence presented was likely to affect the probability of a positive recommendation.

The study concluded that the work of the PBAC was an example of long-term stability and coherence of evidence-based coverage (subsidies) and pricing decisions. Important to this review, it further concluded that the PBAC's willingness to pay was clearly related to the characteristics of the clinical condition and to perceived confidence in the evidence of effectiveness and its relevance, as well as to total cost to government.

The results suggest that decisions by the PBAC had been consistent with its responsibilities as set out in the Act and that other factors beyond cost were regularly taken into account in its decision making.

7.5. Measuring disease burden

7.5.1 Quality-adjusted life years

Change in quality of life is an important outcome considered by PBAC in making its recommendations for subsidisation of medicines. To do this in a standardised way across many different diseases or conditions and patient populations requires measures of quality of life. The most widely used approach for estimating quality of life benefits in economic evaluations is the quality-adjusted life year (QALY).

The QALY considers both the quantity and quality of life generated by the healthcare intervention. It measures adjusted survival time where the adjustment is by means of weighting health-related quality-of-life preferences for specific health states. Expected survival time in each of the health states is adjusted using the preference weights and then summed across the duration of survival to generate expected QALYs gained. The use of preference weights sets QALYs apart from other quality-of-life measures.

QALYs are useful tools in resource allocation (public reimbursement) decisions, allowing for more explicit decisions to be made between healthcare interventions and against new technologies and therapies. With information on the costs and effectiveness of alternative care, an incremental cost-effectiveness ratio (ICER) can be calculated to provide a standard indicator of the additional cost to generate a year of perfect health (one QALY).

QALYs as generally measured, however, may be less sensitive to less severe chronic diseases, and the most commonly used measures from which QALYs are derived have been criticised for not weighing emotional and mental health problems adequately. QALYs are also not designed to take into account the impact on the quality of life of the carer or other family members.

7.5.2 Quality of life

The reference group assessed the evidence presented in the evaluator's report and concluded that, in comparison to more conventional/common conditions, there was still limited formal evidence to demonstrate improvements in quality of life and therefore the comparative value for money of medicines subsidised under the LSDP. The reference group noted that there is literature to show that the medicines have in some instances reversed disease progression. Personal accounts received from patients and carers demonstrated clear health benefits and most reported an improved quality of life.

The need to elevate quality of life as a health benefit or health outcome from receiving treatment from an LSDP-funded medicine was a central thread in the feedback from stakeholders. Many submissions spoke of greatly improved health states such that lives being transformed and patients and/or carers being able to return to relatively normal lives. Quality of life was therefore not insignificant and it should be better acknowledged. The stakeholders also urged the reference group to consider more broadly the societal cost borne by those living with rare diseases or those living with patients with rare diseases. These costs may not be adequately accounted for, if at all, in health cost per QALY based metrics.

The reference group agreed that broader considerations of benefit needed to be considered when assessing the value of medicines for rare disease drugs. The reference group noted that the PBAC has accepted quality-adjusted life years as a key (but not singular) measure of benefit in assessing medicines for public subsidy. In principle, this seemed to be consistent with the interests of the stakeholders. However, the reference group noted that the conditions treated under the LSDP usually resulted not only in shortened life expectancy but also in high levels of disability requiring high levels of carer and community service dependency. Consequently it was important to take a broader societal view and greater consideration of the longer term economic and psychological impact on families and carers. It was noted that while these elements are not inconsistent with the practices of the PBAC there would be benefit in giving greater visibility and weight to these in the decision-making process.

7.6 Pharmaceutical Benefits Advisory Committee rule of rescue and Medicines for Rare Diseases Programme criteria

The reference group and a number of submissions noted the overlap between the criteria used by the PBAC to consider rule of rescue and the criteria for the LSDP. Table 8 contrasts the criteria for rule of rescue, the LSDP criteria and the proposed criteria for the Medicines for Rare Diseases Programme (MRDP). There is significant consistency between the principles of the rule of rescue and the MRDP, although the MRDP criteria are more specific. The notable differences are the explicit recognition of uncertainty of benefit in the proposed MRDP and the requirement that there be a commitment to address this. Moreover, the rule of rescue makes no mention of quality of life as a consideration. In practice the rule of rescue has only been applied to conditions where the likely survival without treatment is very short, whereas in the case of conditions for which medicines are listed on the LSDP survival may be decades even without treatment. If the revised criteria for the MRDP are adopted, there will be specific consideration of impact on quality of life at least as reflected

in level of disability. The reference group decided that the rule of rescue could not subsume the MRDP and that the MRDP criteria were necessary.

Table 8: Comparison of Pharmaceutical Benefits Advisory Committee rule of rescue, Life Saving Drugs Programme criteria and proposed Medicines for Rare Diseases Programme criteria and conditions

Rule of rescue criteria	LSDP criteria and conditions	Proposed MRDP criteria and conditions
• No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients. • The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in the consideration by PBAC. • The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances. • The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by PBAC.	**A)** The drug must be found to meet each of the following criteria: 1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration. 2. The disease is identifiable with reasonable diagnostic precision. 3. Epidemiological and other studies provide evidence acceptable to the PBAC that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease. 4. There is evidence acceptable to the PBAC to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug. 5. The drug must be accepted as clinically effective, but rejected for Pharmaceutical Benefits Scheme (PBS) listing because it fails to meet the required cost-effectiveness criteria. 6. There is no alternative drug listed on the PBS or available for public hospital in-patients which can be used as life-saving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP.	The drug must be found to meet each of the following criteria: 1. There is a rare but clinically definable chronic progressive disease for which the medicine is registered for that indication by the Therapeutic Goods Administration. 2. The disease is identifiable with reasonable diagnostic precision. 3. Epidemiological and other studies provide sound scientific evidence that the disease causes a significant reduction in age-specific life expectancy for those suffering from the disease *or significant ongoing disability* such that the patient would not live independently once the disease was fully manifest. 4. The PBAC considers that based on sound scientific evidence it is more likely than not that a patient's lifespan will be substantially extended or the level and duration of disability substantially reduced as a direct consequence of the use of the drug. 5. That it would not be practical to confirm this through further studies within 5 years because of the rarity and rate of progression of the disease. 6. There is no alternative medicine listed on the PBS or available for public hospital in-patients which can be used as effective treatment for the disease. However, the availability of an alternative medicine under the MRDP

	7. There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition. 8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in one year for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian. **B)** Consideration and advice will also be provided by the PBAC, if applicable, on: 1. The proposed price of the drug compared with the effective price of the drug in comparable overseas markets. 2. The proposed cost of the drug compared with the cost of comparable drugs, if any, that are already funded through the LSDP.	does not disqualify the proposed medicine from consideration for the MRDP. 7. There is no alternative non-medicine therapeutic modality (e.g. surgery, radiotherapy) which is recognised by medical authorities as a suitable and cost-effective treatment for this condition. 8. The cost of the medicine, defined as the cost per dose multiplied by the expected number of doses in one year for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian. 9. The sponsoring company demonstrates it is undertaking an ongoing programme to clarify the clinical benefits or agrees to actively participate in and financially support such a programme.

7.7 Data collection framework

7.7.1 Need for data collection

All parties acknowledged that rare diseases are plagued with lack of information, whether about the natural history of the disease, the clinical evidence, the possibility of dose variation or some other element. There was a general consensus that more systematic collection of data would assist in this area. Increased information would assist in managing the costs of the medicines and add information and evidence about health benefits, the need and frequency of administrating the treatment, dosing by body weight, the therapeutic equivalence where more than one medicine in the same class is available, and clarification of when patients are not responding to treatment.

The reference group sought views from the public on how clinicians and/or companies may be encouraged to fill in the information gaps and to what extent public subsidy of the medicine should be tied to companies and/or clinicians undertaking the research.

Public submissions received and separate stakeholder comments at the Consumers Health Forum of Australia (CHF) facilitated workshops indicated broad support for collecting data on rare disease. This was also substantiated in the CHF-led online survey. The CHF report on

terms of reference 4 and 7 is available at **Appendix B**. Stakeholder sentiments on data collection are also discussed at item 6.3.10 of this report.

There was support to obligate persons receiving treatment to contribute to the data collection registry, but stakeholders noted that this would not absolve the custodians of the registry from prior informed consent and safeguarding the patients' privacy.

Clinicians were generally overcommitted, time poor and/or already doing research in their specialist field. Adequate resourcing was an impediment to having and maintaining data registries that are robust, hold accurate and up-to date-information and are consistent across all jurisdictions. Consumers were in favour of sponsors partnering with government to resource and collect data. This may come in the form of a levy or part of a managed entry scheme for the drug. Data entry personnel to shift the burden from clinicians or nurses could be included as part of the medicine entry/subsidy package. Tripartite partnerships between governments and private or non-government entities were also suggested, though consumers had no agreement on who might be suited to make up-front investment or maintain the registries once established.

Consumers were wary of entrusting commercially focused medicine sponsors or other private entities with personal data and other information held in registries. Legal implications about private ownership of pharmaceutical company held information and reluctance to share what may be proprietary data were issues of concern.

7.7.2 Drug surveillance registry or rare diseases registry

Chapter 7 of the evaluator's report provides a high-level summary of key concepts for collecting data for rare diseases in Australia. According to Gliklich et al (2014) there are four key purposes of a rare diseases registry:

- connect affected patients, families and clinicians
- study the natural history of a disease
- support research
- establish a patient base for evaluating drugs.

The objectives of a drug surveillance registry, on the other hand, are to:

- verify the initial and ongoing eligibility of patients receiving subsidised medicines against the eligibility criteria proposed for the subsidisation
- measure the costs of the drug, as well as the management of the medicine subsidy program
- evaluate the safety and effectiveness of a drug, particularly against the claims that were made during the process by which the medicine was initially approved for subsidisation
- use cost, and measures of safety and effectiveness, to provide mechanisms to support outcome-based risk-share arrangements between sponsors and government that may facilitate the reimbursement of medicines when precise estimates of value are unavailable at the time of 'listing'.

It is important to be purposive about the data collected, as the purpose of the registry would affect how, what, and when the information is collected. In cases where there are uncertainties regarding aspects of the safety, clinical effectiveness and cost offsets of the

medicines considered eligible for the LSDP, the development of a drug surveillance registry tailored to address these uncertainties would be valuable. This type of data collection would support managed entry or performance-based risk-share arrangements. Claims that are made with regard to the safety and clinical effectiveness of the medicines in terms of individual patients' responses to the treatment, at the time of seeking reimbursement, could be verified. To some extent eHealth records may provide a cost-effective and accessible solution to rare disease data management.

Table 9 below lists data collection elements for a drug surveillance register.

Table 9: Proposed data elements for a drug surveillance register

Data category	When it should be collected	When not necessary
Patient/guardian consent	Always. The extent of the consent (whether the patient/guardian opted out of any data collection) and the currency of the consent (a history of all of the versions of consent forms that have been signed) should be stored.	Ongoing consent forms may not be necessary if data collection ceases after initial eligibility or the nature of the data collection or use of the data remains unchanged.
Initial eligibility	Initial eligibility should always be ascertained for each patient at application. Supporting documentation should be provided; however, the collection of specific data points will only be necessary if required to establish ongoing eligibility or the effect of the drug.	–
Ongoing eligibility	The disease can progress to a point where treatment is no longer effective or there is no evidence or clinical plausibility for ongoing benefit. Supporting documentation may be required to establish that the disease has not progressed to a 'no treatment' stage. Ongoing eligibility must always be captured if there is a risk that the disease could progress such that the treatment has a negative benefit–risk balance.	The drug has established adequate efficacy regardless of stage of disease. Negotiations with the sponsor have resulted in a price commensurate with the drop in efficacy in patients who progress.
Baseline and follow-up surrogate measures of effectiveness/ safety	Disease improvement or stability is determined by comparing with baseline markers (e.g. haematological, biochemical, organ size, neurological function). The agreed price of a drug is linked to outcomes achieved in patients taking the drug through a managed entry arrangement.	No ongoing eligibility criteria are required and no managed entry scheme requiring the measurement of effectiveness has been entered into.
Dose and frequency	This should routinely be provided by the treating clinician for all patients who require any other data to be collected. If no other data is captured, dose and frequency could be sought from another source.	–
Monitoring and major intervention costs	The cost of monitoring patients (i.e. scans, biopsies, specialist visits) receiving the drug is expected to be high (relative to the cost of the drug). These additional costs are unknown or not accounted for at the time of the decision to reimburse the drug. The Department of Health would seek to renegotiate with the drug sponsor if these costs were greater than expected. This may form part of a managed entry arrangement. Interventions (hospitalisation, transfusions, organ transplants, medications) are expected to be avoided or reduced in frequency while on the drug. The Department would seek to renegotiate if costs associated with these interventions were greater than expected. This may form part of a managed entry arrangement.	The cost of monitoring the use of the drug is unlikely to be substantial. The reduction in interventions claimed at the time of the decision to reimburse the drug is likely to be met, or unlikely to impact on the overall cost of treatment. The ongoing price of the drug to the Government is not linked to other costs or will not be renegotiated on this basis.

Data category	When it should be collected	When not necessary
Baseline and follow-up patient/carer reported wellbeing	Improvement of quality of life or pain is an important outcome for the drug, and the agreed price of the drug is linked to a stabilisation or improvement in these outcomes.	Patient-reported outcomes do not make up the claim of effectiveness for the drug. Price is not linked to establishing an improvement or stabilisation for this outcome.
Death	This should be sought for all patients. However, while it may be requested from the data provider, it may prove difficult to capture reliably. Alternative sources for date and cause of death should be sought.	–

Table 150, cited on p. 283 of the evaluator's report.

As described above, the objectives of a rare disease registry data are different, and therefore data collected may not be suitable for determining the comparative clinical effectiveness of different medicine treatments. That is the role of randomised controlled trials. However, in cases where there are no alternative treatments that improve patient survival and where there is good information on the natural history of the condition, a drug surveillance registry may be a viable option for confirming the safety and clinical effectiveness of a subsidised medicine treatment. It would be important to ensure that the drug surveillance registry were developed to answer specific questions and that the appropriate governance, technical arrangements and resourcing are in place before commencing data collection. Any registry should be able to tap into evidence generated overseas. Hence it would be important to agree upon standards to ensure consistency and accuracy.

Overall, as summed up in one submission, rare diseases that require highly expensive medicines should require clinical justification for Commonwealth funding for commencement of treatment and, following regular evaluation of therapy outcome, ongoing funding.

The reference group noted that there are many registries in Australia and internationally for patients with rare diseases. Indeed in some cases there is more than one registry for the same disease. The reference group noted the work on the development of registry software framework that facilitates the development of separate registries with common features (Bellgard MI, Rendon L, Radochowski M, Hunter A, 'Second generation registry framework' *Source Code for Biology and Medicine* 2014:9:14). Such registries can then be readily networked such that patients can agree to be listed on multiple registries seamlessly. This framework has been has been deployed by WA Health, although it is still a work in progress.

Section 8: Proposed administration of the Life Saving Drugs Programme

The administrative arrangements for the LSDP rely heavily on the direct involvement of Canberra-based Commonwealth public servants who otherwise have no involvement in patient care. The reference group noted that this is not consistent with good clinical care management. It is also inconsistent with the division of responsibilities between the Commonwealth and the states and territories for health service delivery, given that the majority of these patients are seen in public sector services.

The reference group noted the wide support for the re-establishment of the disease advisory committees but also noted that these committees convened on a national basis and that, while they were disease specific, membership substantially overlapped. Given the potential for a growing number of diseases and treatments seeking public funding, the reference group did not consider that this approach would be sustainable. However, the reference group contended that clinical oversight in all decisions related to patient care is essential, more particularly for borderline cases. This may be provided through the responsible clinician with advice as appropriate from relevant subject matter experts.

The reference group recommended a closer look at the establishment of a small number of centres of clinical expertise (CoEs) in rare diseases, where the larger states network with smaller states or territories for clinical visits. Such an approach could also form the basis for more effective disease registries, where different centres might take responsibility for one or more different diseases. Such CoEs are expected to build upon existing state hospital structures similar to that for inborn errors of metabolism. A registration process for physicians attached to the CoE, similar to that for the approved metabolic specialists for the Inborn Errors of Metabolism Programme could be examined. As noted in a number of submissions, such CoEs already exist in de facto form, as care of most people with rare diseases is limited to a small number of centres and clinicians, usually based in one of the large children's hospitals. Designation as CoEs would be a recognition of this important role.

Additionally there is benefit in having multi-stakeholder discussions prior to former evaluation of the medicine for funding to assist in the submission. These discussions would be used to discuss whether the medicine meets the requirements for a rare disease therapy subsidy, clarify evidentiary requirements, determine appropriate initiating or continuation treatment rules, and identify appropriate patient population or to provide the patients' testimony or impact statement of the health outcomes. This represents the first additional stage of a two-step assessment process proposed by stakeholders.

The reference group also recommends that, as part of the usual Pharmaceutical Benefits Advisory Committee (PBAC) assessment process, when a medicine is to be considered under the Medicines for Rare Diseases Programme (MRDP), the current Economic Sub-Committee (ESC) would be supplemented by relevant clinical specialists (i.e. an expanded Economics Sub-Committee, ESC+) for consideration of that medicine to assist in framing advice to the PBAC. This represents the second additional step of the medicine evaluation process. Similar to ESC and the Drug Utilisation Sub-Committee, this committee would not have voting rights on the funding decision. Its primary role would be to advise on appropriate levels of

evidence, funding options, future likely treatments and potential impacts on the health system, and also recommendations on agreed levels of evidence acceptable in advance of clinical trials.

The PBAC would retain responsibility for recommending appropriate indication and target populations for the medicine in question to the Minister. Mirroring section 100 medicines listed on the PBS, administration of the intentions of the PBAC decisions would be the responsibility of the Department of Human Services (Medicare).

8.1. Steps to transforming the Life Saving Drugs Programme into a section 100 Medicines for Rare Diseases Programme

The reference group noted that, if the decision is made to create a section 100 MRDP, it will be important to ensure that, prior to cessation of the LSDP, arrangements are in place to ensure:

- there is no disruption in supply to patients of the currently subsidised medicines for rare diseases
- existing patients, their carers and their clinicians are made aware of the proposed changes and reassured that access will continue
- the rare diseases community more broadly is informed of the changes.

8.2. Integrating the section 100 Medicines for Rare Diseases Programme into the Pharmaceutical Benefits Advisory Committee process

The proposed process for application under the new PBS Medicines for Rare Diseases Programme would be aligned to the existing PBAC cycle with the following steps.

1. Pre-submission discussion between the company and the Pharmaceutical Evaluation Branch (PEB). As distinct from the usual PBAC process, this would be a mandatory step.
2. Pre-submission stakeholder meeting organised by the PEB, including relevant clinical experts. This meeting would clarify treatment guidelines from a PBAC perspective including specific diagnostic criteria, eligibility requirements, dosing and other therapeutic considerations and, where relevant, stopping rules. Patients, carers and families would have an opportunity to present their perspective. This would also provide an opportunity for patients, carers and families to be fully informed of the benefits and limitations of medications.
3. Approval to submit under the section 100 Medicines for Rare Diseases Programme (i.e. the condition and medicine meet the programme eligibility criteria) agreed by the Pharmaceutical Benefits Advisory Committee executive.
4. Formal submission to PBAC, followed by the usual cycle.
5. ESC+ meeting considers the application as part of the usual cycle.

In considering the application, the PBAC would need to resolve that the condition and medicine met the requirements of the MRDP and were not more appropriately subsidised under another programme, and that, in the broader context, the PBS was affordable.

Appendices

Appendix A Life Saving Drugs Programme Reference Group issues paper

Appendix B Consumers Health Forum report

Appendix C Adelaide Health Technology Assessment report

Appendix D Summary of the 2014 public consultations

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Abbreviations

AHTA	Adelaide Health Technology Assessment
CHF	Consumers Health Forum of Australia
CoE	centre of rare disease expertise
DACs	disease advisory committees
DUSC	Drug Utilisation Sub-Committee
ESC	Economics Sub-Committee
HSDP	Highly Specialised Drugs Programme
LSDP	Life Saving Drugs Programme
MCDA	multi-criteria decision analysis
MRDP	Medicines for Rare Diseases Programme
NICE	National Institute for Health and Care Excellence (UK)
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
QALY	quality-adjusted life years
TGA	Therapeutic Goods Administration