Patients diagnosed with rare diseases face shortened life expectancy, significant morbidity, chronic disability and limited viable treatment options. When effective treatments are available there are financial challenges to achieving access on an individual basis which underlines the critical need for government subsidy.

Rare disease therapies have a number of unique considerations compared to therapies for more prevalent conditions, including smaller and more heterogeneous patient populations and limitations on data to characterise the natural history of the disease. In addition, the rarity of these conditions generally mean different trial designs are necessary and therefore appropriate *eg.* single arm studies, use of surrogate endpoints appropriate for rare disease and limited long-term follow-up. Frequently there is a lack of broad understanding of disease and its impact on the patient and carer. In Australia, decisions about the funding of rare disease therapies are further challenged with the legislative requirement to evaluate the cost-effectiveness of new therapies.

As part of the post-market review of the Life Saving Drugs Programme (LSDP), a Rare Disease Industry Working Group (RDIWG) was established to formulate recommendations from the perspective of potential sponsors of rare disease therapies. These recommendations have looked at the overall funding structure for products used in the treatment of rare disease and potential process improvements for the assessment of these products.

Now as part of the current PBAC guidelines review, the RDIWG has developed potential guidelines, should the Government determine through the ongoing LSDP Review, to move the funding of these products into the Pharmaceutical Benefits Scheme. This work has been conducted through a multi-stage review and development process with the key results outlined below:

Development of a framework for consideration of amended PBAC guidelines for rare disease therapies (Appendix I).

Current challenges identified by the RDIWG include: obtaining appropriate advice and guidance upfront; communicating the burden of disease; reliance on lower levels of evidence; challenges in demonstrating cost-effectiveness; transparency of decision making.

The RDIWG recommends the following framework for rare disease therapies:

1. Establishment of a fit-for-purpose process for PBAC applications for reimbursement of rare disease therapies including comprehensive guidelines for the generation of such applications.
2. Establishment of a rare disease subcommittee or advisory committee of PBAC to provide specific guidance for rare disease therapy submissions.
3. Establishment of a fit-for-purpose pre-submission process including, where appropriate, a stakeholder meeting made up of Department of Health representatives, clinicians with expertise in the specific rare disease under consideration, Sponsor company(ies) and rare disease patient representatives. This process would also determine eligibility to be assessed under a 'fit-for-purpose' rare disease pathway.
4. Any Managed Access Programmes for rare disease therapies should follow the framework devised by the Access to Medicines Working Group (AMWG). In addition relevant appropriate clinical experts should be consulted when negotiating the Deeds of Agreement for such programmes to ensure that all parties (the treating clinician, patient and sponsor) are able to comply with the terms of the agreement.

An international review of health technology assessment (HTA) guidelines for rare disease therapies (Appendix II).

Through a review of guidelines for rare disease therapies from England, Scotland and Canada – several themes emerged: early engagement via an established pre-submission process; flexible evidentiary requirements and cost-effectiveness criteria; a clear decision making framework; a formalised stakeholder engagement framework; clarity in decision making and funding decisions.

Recommendations for PBAC Guidelines for rare disease therapies to form part of revised PBAC guidelines once finalised.

The content below reflects RDIWG recommendations for guidelines specific to rare disease therapies. These have been developed using findings from both stages outlined above and are intended to form a new section of Part B of version 5.0 of the PBAC guidelines.

The amended guidelines will inform assessment of rare disease therapies within a new legislative framework, drawing from international experience utilising some of the themes described above, and in particular, including a dedicated pre-submission process. Most importantly, the guidelines and process should recognise that rare disease therapies have a number of differentiating characteristics which cannot be considered solely through the process and guidelines for therapies for non-rare conditions.

Key points

- The RDIWG supports an amended, flexible, 'fit for purpose' assessment process for rare disease therapies that considers multiple data sources and reflects the extent of knowledge of the disease at the time of submission.
- The RDIWG supports the involvement of clinical experts and patients in the value assessment of rare disease therapies on a consistent basis.
- The RDIWG supports the inclusion of a new section of Part B of the PBAC guidelines dedicated to rare disease therapies.
- The RDIWG recommends the Department of Health establish a working group to facilitate further developing guidance for rare disease therapies.

Recommendations to inform a new section of Part B v5.0 of the PBAC guidelines (Product type 5 – therapies for rare diseases).

Introduction

This draft subsection applies to a submission for a pharmaceutical product to treat a rare disease.

This guidance applies to a submission for a rare disease therapy seeking listing under the PBS or seeking funding through an alternative program (to be determined as part of the LSDP review). The additional draft guidance is not exhaustive and provides context for the specific circumstances of assessing a therapy for a rare disease.

P5.1 Section 1

General guidance

- Describe the rare disease context. This may include:
    - The natural history and implications of small patient numbers.
    - Any heterogeneity of disease trajectory, despite the small patient population.
    - The availability of published registries, case series or other studies.
- Describe the timing of diagnosis and the criteria used. Indicate if the initial diagnosis is part of a national or state screening programme (*eg.* Neonatal screening).
- Describe the treatment pathway in Australia. If relevant, this should include outlining any constraints or special considerations such as geography, referrals for diagnosis, monitoring or treatment, paediatric considerations, special needs etc.
- Describe the burden of illness or severity of the medical condition treated.
- Identify where clinical experts have been used to inform this section.
- Patient and consumer input can be used to inform disease context and rationale for PBS listing.
- Address the rationale for any proposed monitoring requirements and/ or a Managed Access Programme, if applicable.
- Where appropriate, use the agreed principles and outputs from the advisory group and/or stakeholder meeting.

Specific guidance

<u>Clinical issue (Subsection 1.1)</u>

In addition to specific information requested for this section, present information to justify the disease meets the rare disease prevalence criteria.

In detailing the burden of disease, highlight any expected reduction in life expectancy due to the disease. Registry reports or similar may be useful in this regard, recognising that such evidence may need to be sourced internationally given the rarity of the disease.

Provide an overview of the quality of life of patients living with the rare disease.

If relevant, provide an overview of the impact on family and carers. An understanding of the impact on patients and carers is particularly important where the rare disease may not be well understood, noting carers can be substantially impacted by caring for patients with rare diseases.

Within *Relevant subpopulations*, highlight heterogeneity in the target Australian population including demographic factors (such as age and gender) and clinical factors (such as severity, time since diagnosis, body system involvement). If heterogeneity is likely to be an issue, this should be linked to

the interpretation of the clinical evidence presented in Section 2. Where unexplained heterogeneity in the natural history or rate of progression of disease exists, this should be discussed.

Clinical management algorithm (Subsection 1.2)

Gathering expert advice is likely to be integral to developing the local clinical management algorithm for rare diseases (see P5.5.2.).

In situations where clinical management was discussed as part of an advisory group and/or stakeholder meeting, use any agreed principles emanating from these meetings.

A description of the treatment pathway may include:

- Who treats the disease and where, *ie.* Whether treatment is limited to a single centre of excellence or treated in multiple centres.
- A description of how many clinical experts treat patients in Australia.
- A description of how and where patient subgroups such as adults and children are treated.
- If appropriate, medical or surgical interventions as a consequence of the disease should be discussed.

In order to describe the treatment pathway, clinical registry information may be used, where appropriate. When using registry information, report the proportion of the target population that is included in the registry.

Proposed PBS listing (Subsection 1.4)

If the sponsor proposes to use a Managed Access Programme to address clinical uncertainties, this should be detailed in this section. Sponsors should be guided by the AMWG Framework. Elements of a Managed Access Programme may be discussed during the advisory group and/or stakeholder meeting.

P5.2 Section 2

General guidance

- It is acknowledged that randomised trial evidence is generally not available for rare disease therapies and sponsors should seek to contextualise the available evidence.
- Patient and consumer input can be used to inform and contextualise clinical evidence.
- In the absence of comparative data, sponsors may wish to collect data for the purposes of understanding the natural history of the disease for the submission from registries, grey literature, chart reviews and clinical experts.
- Provide an assessment of efficacy in relation to the nominated comparator using a methodology which is appropriate for the available evidence. Focus on minimising uncertainty through the use of complementary methods where possible.
- It is acknowledged that clinical practice for rare diseases are evolving over time, and therefore, clinical guidance is needed in relation to the most appropriate clinical measures to support a superiority or non-inferiority claim – which underpins economic evaluations.
- Use a clinical expert to address trial applicability where appropriate.
- Link the therapeutic conclusion to information presented in Subsection 1.1 addressing the rationale for PBS listing.
- Where appropriate, use the agreed principles and outputs from the advisory group and/or stakeholder meeting.

Specific guidance

Literature search methods and identifying relevant trials (Subsections 2.1 and 2.2)

Follow the general guidance for use of *nonrandomised studies* when presenting nonrandomised studies for rare disease therapies.

In order to provide comparative data it is acknowledged that sponsors may need to rely on unpublished registry information, grey literature, chart reviews, clinical expert opinion or naïve indirect comparisons of nonrandomised studies for two or more therapies. If this information is collected for the purpose of the submission, append a report detailing the methodology used to collect the information. When using registry information there is likely to be a preference for registries affiliated with appropriate medical colleges, professional societies, official patient organisations, regional/national health services or international collaborations.

Trial execution and design (Subsection 2.3)

Provide details of the characteristics of nonrandomised trials or registries, including the extent of coverage and applicability to the proposed patient population. Other characteristics may also be relevant, such as timing of entry into the registry (diagnosis vs first symptoms), frequency of data collection, availability of genotype data, relevance to contemporary clinical management and birth cohort heterogeneity.

Trial characteristics (Subsection 2.4)

It is acknowledged that clinical practice is evolving over time, and therefore, defining a minimal clinically important difference (MCID) is difficult in rare disease therapies. In cases where a MCID is difficult to determine, follow the general guidance in Appendix 3 under *Situations where the MCID is difficult to determine*. Where appropriate, use agreed principles and outputs from the advisory group and/or stakeholder meeting.

Trial results: whole trial population (Subsection 2.5)

It is acknowledged that cross-sectional quality of life data may not provide useful information for rare disease therapies as patients may exhibit 'response shift'[1] which can impact standard psychometric indices, such as reliability and validity. This can be more apparent in chronic conditions that manifest in early childhood – as is the case with many rare diseases. Consider linking the information presented in Subsection 1.1 with quality of life over the patient lifetime.

Trial results: additional analyses (Subsection 2.6)

To support a superiority or non-inferiority claim, it is acknowledged that sponsors may need to present indirect comparisons based on nonrandomised studies and other diverse data sources with no common references. An example includes data from a single-arm trial and comparative data from registries, grey literature, chart reviews or clinical experts.

In such situations, it is recognised that indirect comparison methodology such as Bucher single pairwise method, matching-adjusted indirect comparison (MAIC), simulated treatment comparison (STC), network meta-analysis (NMA) or mixed treatment comparison (MTC) may not be appropriate nor practical. To account for limitations in the data and small patient numbers, the sponsor may wish to present simple comparative methodologies such as naïve comparisons and benchmarking with historical cohorts noting that these methods are prone to bias. In particular, use caution in matching clinical trial data with historical control data and should be mindful of the different settings (clinical trial conditions versus real world), frequency of follow-up, inclusion criteria and differences in outcome definitions and reporting.

In reporting naïve indirect comparisons, use the framework provided in *Additional methods to quantify results*. Attempt to verify any comparison through complementary methods where appropriate.

---

[1] Cohen JS & Biesecker BB. Quality of life in rare genetic conditions: a systematic review of the literature (2010). Am J Med Genet A. 152A(5):1136-56.

Applicability of the trial evidence (Subsection 2.7)

To address applicability follow the general guidance in Subsection 2.7 where feasible. However it is acknowledged that including studies with small sample size may not permit an appropriate assessment of treatment effect variation, and may lead to spurious findings. Therefore, the sponsor may wish to include a report from a clinical expert detailing the applicability of the evidence to the local treatment pathway and patient population (see *P5.5.2 Gathering expert opinion*).

P5.3 Section 3

General guidance

- A fit-for-purpose cost-effectiveness analysis should be presented to support a superiority argument in Section 2.
- Contextualise the available model inputs and the need for a flexible assessment approach for the rare disease. For instance:
    - In accordance with the guidance in Section 3, the sponsor has the flexibility to present a cost-effectiveness analysis where circumstances prohibit a cost-utility analysis.
    - In situations where there is a lack of rigorous data to permit constructing a methodologically robust cost-effectiveness model, consider a simple, pragmatic and fit-for-purpose economic model.
- Identify where clinical experts have informed the model, where applicable.
- Where appropriate, use the agreed principles and outputs from the advisory group and/or stakeholder meeting.

Overview and rationale of the economic evaluation (Subsection 3.1)

Subsection 3.1 currently provides flexibility with the methodological approach which can include a cost-effectiveness analysis and/or a cost-utility analysis. For rare disease therapies, it is acknowledged that the sponsor may not have access to data to permit the construction of a rigorous cost-effectiveness model. Further, there may be a lack of information to estimate quality of life utility values, and therefore, cost-utility analysis may not be appropriate. In these cases, consider a simple, pragmatic and fit-for-purpose economic analysis which is consistent with the general guidance provided under Subsection 3.1.

As rare diseases are likely to have non-health implications (such as production changes), consider presenting a supplementary cost-benefit analysis (see *P.5.5.4 Including non-health (societal) outcomes*).

Rare diseases often have broad societal implications beyond the health system including the ability of patients and carers to work, the cost of treatment (and travel to specialised treatment centres) and some of the intangible implications such as the pain and suffering caused by the disease. Therefore, sponsors should consider adopting a societal perspective in a sensitivity analysis (see *P5.5.4 Including non-health (societal) outcomes*).

Where patients receive lifetime therapy, as is often the case for childhood-onset rare diseases where the benefit is realised well into the future, the discount rate is likely to have a discernible impact on the cost-effectiveness result. Therefore, consider varying the discount rate in a sensitivity analysis.

Computational methods and structure of the economic analysis (Subsection 3.2)

Rare diseases are likely to have similar or greater complexity compared to diseases for more prevalent conditions. In situations where there is a lack of rigorous data to permit construction of a methodologically rigorous cost-effectiveness model, consider a simple, pragmatic and fit-for-purpose economic analysis.

In situations where there is considerable heterogeneity in the patient population, an individual-level (or microsimulation model) may help address this. However, consider if the justification for presenting a microsimulation outweighs the additional complexity.

For models addressing rare diseases, it is likely expert opinion will be needed to provide assumptions (see *P.5.5.2 Gathering expert opinion*).

Transition probabilities (Subsection 3.4)

Surrogate markers are often necessary primary outcomes in clinical trials of rare diseases. Guidance provided is in Subsection 3.4 states *'it may not be necessary to fully detail the transformation of a proposed target clinical outcome'*. This reflects cases where the PBAC has previous accepted the surrogate outcome as valid and all of the following apply:

- *The proposed treatment effect is within the range of the comparative treatment effect previously identified in the clinical evidence associated with transformation.*
- *The proposed medicine will be used in the same population as the previously accepted transformation.*
- *The medicines in the evidence used to previously validate the surrogate, the main comparator and the proposed medicine are all in the same class or have a similar mechanism of action.*

The PBAC has adjudicated on many surrogate markers and sponsors should weigh up the additional information gained from following the framework presented in Appendix 7 versus the uncertainty generated. If applicable, use the agreed principles and outputs from the advisory group and/or stakeholder meeting.

Health outcomes (Subsection 3.5)

If a cost-effectiveness analysis is chosen, consider a clinical endpoint which has been adjudicated by the PBAC in the context of rare disease therapies, such as FEV_1 or Six Minute Walk Test (6MWT)[2]. In some cases, the choice of a clinical endpoint will need to be balanced against the need to reflect multi-systemic disease and appropriately represent the disease pathway.

P5.4 Section 4

General guidance

- Contextualise the budget impact model inputs and the need for a flexible assessment approach for the rare disease. For instance:
    - The need for ongoing patient monitoring.
    - The need for patient support services or Quality Use of Medicine activities.
- Identify where clinical experts have informed the budget impact model, where applicable
- Where appropriate, use the agreed principles and outputs from the advisory group and/or stakeholder meeting.

P5.5 Other information

P5.5.1 Managed Access Programme

If the sponsor proposes to use a Managed Access Programme to address clinical uncertainties, sponsors should be guided by the AMWG Framework.

P5.5.2 Gathering expert opinion

[2] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product

It is acknowledged that applications for rare disease therapies often rely on 1-2 clinical experts who may have been involved in drug trials and often are part of sponsor's advisory board. However this should not preclude sponsors using clinical experts so long as any potential conflicts are declared. In general sponsors should follow the general guidance provided in Appendix 1 in relation to expert opinion. Sponsors should seek to contextualise the available pool of clinical experts to ensure PBAC understands the nature of the advice being provided.

P5.5.3 Surrogate to final outcomes

Sponsors should weigh up the additional information gained from following the framework presented in Appendix 7 versus the uncertainty generated.

P5.5.4 Including non-health (societal) outcomes

Rare diseases often have broad societal implications beyond the health system which impact patients, carers, communities and the broader society. In this way, the voice of patients and/or carers is likely to be central to applications for rare disease therapies. The patient and/or carer voice can be included in applications in multiple ways including via patient and or carer preferences, willingness to pay or production changes.

It should be noted that discrete choice methodologies can be utilised to estimate patient or carer preferences in rare diseases and the introduction of best/worst scaling can help address issues of sample size. In addition, multi-criteria decision analysis has been proposed as an alternate method to estimate preferences[3] which may be useful in dealing with small sample sizes.

[3] Ijzerman MJ, van Til JA and Bridges JFP. A Comparison of Analytic Hierarchy Process and Conjoint Analysis Methods in Assessing Treatment Alternatives for Stroke Rehabilitation (2012). The Patient – Patient-Centered Outcomes Research. 5(1):45-56.

Appendix I

Framework document_26MAR15_

Appendix II

International rare disease guidelines_Ja