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Funding
Rare Disease Therapies
in Australia

**ENSURING EQUITABLE ACCESS
TO HEALTH CARE FOR ALL AUSTRALIANS**

NOVEMBER 2014

About the
McKell Institute

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Contents

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1. Executive Summary

Australia's system for funding new therapies that treat rare diseases is in need of reform.

As recognised when the Life Saving Drug Program (LSDP) was established in the 1990s, there is a need for a fit-for-purpose process to deal with the funding of therapies for rare diseases in Australia.

However in the last 4 years only two new therapies have been approved under Australia's current program for rare disease therapies. One, listed on a cost minimisation basis in a disease area already covered by the scheme and the second having started their listing process before the Government's last review of the program. **Aside from these products, no new treatments for rare disease have successfully navigated the entire process for funding rare disease therapies since the reforms in 2010.[1]**

Australians are not only being denied access to new therapies funded overseas, even when they are provided, they are having to wait much longer. When new treatments for rare conditions are eligible under the Pharmaceutical Benefits Scheme's Highly Specialised Drug Program there are significant delays in patient access and significant access restrictions imposed.

Analysis contained in this report finds that Australians are generally waiting from 2 to 4 years longer for access to rare disease therapies available in comparable countries like the United Kingdom, Canada, Germany and the Netherlands.[2] Some medications remain unavailable 8 years after becoming available overseas. Many rare disease therapies available overseas are unlikely to be available in Australia without policy reform.

The current funding models are no longer fulfilling their intended roles. Many Australians have had to rely on their own/family funds or compassionate

access from pharmaceutical companies to access new therapies. This uncertain environment is not equitable and a more sustainable approach is required.

A new approach is needed that considers the full scope of rare disease management, brings Australia closer to international standards on the definitions of rare diseases and evidence requirements for treatments, and adopts greater flexibility in the assessment of cost-effectiveness.

There is no common definition of a rare disease across the Australian health system. The Therapeutic Goods Act includes a limit of 2,000 patients for the registration of orphan drugs - the equivalent of approximately 1 patient in 10,000 persons.[3] This definition captures fewer rare diseases than in comparable countries. In the United States the definition is 1 in 1,500, in Canada and the European Union it is 1 in 2,000 and in South Korea it is 1 in 2,500.

This report considers current approaches to the funding of rare disease therapies in Australia and internationally, reviews the current and future challenges, and proposes a set of recommendations to guide the future development of rare disease policy in Australia.

The report concludes with consideration of a new approach to funding therapies for rare diseases based on Multi-Criteria Decision Analysis (MCDA), which would better align with Australia's National Medicines Policy and reflect international best practice.

If adopted, the recommendations will ensure more patients diagnosed with a rare disease will have access to the therapies and standard of health care the majority of Australians take for granted.

2. Summary of Recommendations

RECOMMENDATION 1:

The Australian Government should develop a National Strategy for Rare Diseases that provides a holistic approach to rare disease management. This would cover research and development, regulation, diagnosis, treatment, and the funding of new therapies and ongoing care needs of patients suffering rare diseases.

RECOMMENDATION 2:

Australia should be mindful of international practice and developments when designing rare disease policy frameworks. This includes reflecting international developments in the definition of a rare disease, assessment processes, and the evidence requirements for rare disease therapies, to ensure that Australia is a world leader in rare disease therapies and medical innovation.

RECOMMENDATION 3:

A more flexible analysis of cost-effectiveness should be adopted in the assessment of new therapies that balances other considerations such as equity, the rule of rescue, community values, patient needs and the long-term costs avoided as a result of access to treatment. Consideration should be given to using Multi-Criterion Decision Analysis as a decision-making framework with decision weights based on community and patient values.

RECOMMENDATION 4:

The unique nature of therapies for rare diseases, including small patient populations and the implications this has for clinical trials, should be recognised in the evidence requirements for funding. This is necessary to address uncertainty in current processes for the development and funding of rare disease therapies in Australia.

RECOMMENDATION 5:

The process for assessing new therapies for rare diseases should be efficient, fit-for-purpose, transparent and informed by community and patient values. This is necessary to ensure trust and legitimacy of decisions about funding new therapies for rare diseases, that Australians have timely access to critical treatments, and to reflect the importance of medical research and innovation to the Australian community.

These recommendations seek to balance the need for a sustainable and effective process for managing rare disease therapies with the community and social values of equity in access to treatment for rare diseases.

These recommendations are proposed to guide Government policy on the funding of rare disease therapies in a manner consistent with the National Medicines Policy objective below.

OBJECTIVE ONE:

Timely access to the medicines that Australians need, at a cost individuals and the community can afford.

The unique nature of therapies for rare diseases, including small patient populations and the implications this has for clinical trials, should be recognised in the evidence requirements for funding

More flexible analysis of cost-effectiveness should be adopted that balances other considerations such as equity, the rule of rescue, community values, patient needs and the long-term avoided costs of access to treatment.

The process for assessing new therapies for rare diseases should be efficient, fit-for-purpose, transparent and informed by community and patient values.

OBJECTIVE TWO:

Medicines meet appropriate standards of quality, safety and efficacy.

The unique nature of therapies for rare diseases, including small patient populations and the implications this has for clinical trials, should be recognised in the evidence requirements for funding

OBJECTIVE THREE:

Quality use of medicines.

The Australian Government should develop a National Strategy for Rare Diseases that provides a holistic approach to rare disease management.

OBJECTIVE FOUR:

Maintaining a responsible and viable medicines industry.

The process for assessing new therapies for rare diseases should be efficient, fit-for-purpose, transparent and informed by community and patient values.

Australia should be mindful of international practice and developments when setting rare disease policy frameworks.

3. Introduction

A rare disease is a life threatening or chronically debilitating condition that only affects a very small number of people in the population. Any therapy developed to treat a rare disease thus only has a very limited number of potential patients.

A rare disease is a life threatening or chronically debilitating condition that only affects a very small number of people in the population. Any therapy developed to treat a rare disease thus only has a very limited number of potential patients.

Rare diseases are often life threatening or chronically debilitating and sufferers frequently have no viable treatment options. New therapies for rare diseases may provide the only treatment option for patients and therefore address an unmet medical need.

There is no common definition of a rare disease across the Australian health system. The *Therapeutic Goods Act 1989* includes a limit of 2,000 patients for the registration of orphan drugs - the equivalent of approximately 1 patient in 10,000 persons.[4]

Another definition referred to in Australia is that put forward by the International Conference of Rare Disorders (ICORD). ICORD define a rare disease as 'any disorder or condition that is 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.'[5]

Although these definitions are referred to, they are not universally adopted within the Australian system and may not be reflected in the existing decision making framework for funding of therapies.

Estimates range from 5,000-8,000 known rare diseases. Without improved data, it is difficult to determine the number of people affected by rare diseases, but international estimates have suggested up to 6-8 per cent of the population may be affected.[6]

Just as defining a rare disease is complex, so too is the process for approval and funding of rare disease therapies in Australia.

The Life Saving Drugs Program (LSDP) provides one mechanism for funding new therapies that treat rare and life threatening conditions in Australia.[7] In addition, some therapies for rare diseases are funded under the Pharmaceutical Benefits Scheme (PBS), including through its Section 100 highly specialised drug (HSD) program.[8]

The Minister for Health, the Hon Peter Dutton MP announced a review of the LSDP on 9 April 2014.[9] In announcing the review, the Minister indicated that consideration needed to be given to access and equity, value for money and the future administration of the program.

The review is timely given widespread concerns with the current program.

Often it is families of sufferers of rare conditions that end up bearing the burden of managing the costs of therapy and care, due to the lack of affordable treatments. This burden is excessive, and cannot be fairly managed in any way other

than through the insurance provided by a universal health system.

However, patients are finding that even where new therapies become available overseas, they cannot access them in Australia due to the high cost and lack of government funding.

Patients and their families are frustrated that new therapies funded overseas are not being funded in Australia, restricting access to those with the means to pay themselves. Even where access is granted, patients experience significant delays due to the excessive level of red tape associated with the current system.

Patients living with rare diseases do not have time on their side. They need access to treatments that can stabilise their disease and extend their life expectancy in a much more timely efficient manner than is currently experienced in this country.

Manufacturers who have responded to government incentives in Australia and overseas for greater research into rare diseases are now finding that the Government is unwilling to fund the therapies that have been developed. This commercial uncertainty is placing future research and the marketing of existing therapies for rare diseases in Australia in jeopardy.

The process for listing a new therapy often involves making multiple submissions to Government, which adds to the costs of bringing new therapies to market and creates additional uncertainty for both patients and manufacturers.

While many manufacturers have been willing to provide compassionate access to new therapies, this is usually intended to cover the period between registration and public reimbursement and not to continue indefinitely.

The Government is dealing with growing budget pressures, including from an ageing population. Public campaigns to fund new therapies for rare diseases add to the budget pressures, and where such therapies do not meet standard cost-effectiveness criteria these decisions become increasingly difficult to justify in terms of the overall health budget.

At the same time, the Government is looking to new effective therapies, including for rare diseases, and approaches to managing health costs, in order to take pressure off the health system.

The new Medical Research Future Fund would drastically expand publicly funded research in Australia and could lead to new treatments for rare diseases. However, without a system to commercialise and ensure access to these therapies if they are developed, the fund may not deliver on its promise.

The current system also risks creating repeated scenarios of drugs being funded on the basis of successful media campaigns rather than on clearly defined and transparent criteria.

Consistent with the National Medicines Policy,[10] a new approach is required that ensures the funding

of new therapies for rare diseases is underpinned by the principles of effectiveness, efficiency and equity.

Reforms are needed to provide greater certainty and transparency to patients, clinicians and industry, reduce red tape and delays in access to new therapies, and ensure both equitable treatment of patients and the sustainability of government finances.

This report sets out the current Australian policy for funding rare disease therapies and considers this in the context of Australia's universal health care system.

The international context is then explored, including the approach to rare disease therapies used in other developed countries, such as the United Kingdom, Canada, South Korea, Germany and the Netherlands.

Current policy issues with the operation of Australia's rare disease policies are then outlined, including budget sustainability and the impact of the 2010 reforms on patient access.

Future policy challenges are also addressed, covering the ageing of the population and the impact new personalised medicines on current funding approaches.

An ethical framework for developing a policy framework for rare diseases is then discussed.

The report then provides an overview of the policy objectives to fund new therapies for rare diseases, and how a different approach is required to meet the objectives of the National Medicines Policy. This includes outlining the ethical issues created by a focus on cost-effectiveness when dealing with therapies for rare diseases.

The report concludes with a proposed way forward, including recommended principles to guide the development of future rare disease policy in Australia.

Raymond's story

Meet Raymond, also President of the Australian Pompe's Association who works tirelessly with and on behalf of the members and families. Raymond tells his story.

I am a 62-year-old, late onset Pompe patient, with a loving wife and daughter. I was diagnosed in 2002 after years of failing health.

I started receiving a treatment with a new innovative therapy in February 2007, under the International Compassionate Access program that had been established by the company which makes this drug. Prior to starting treatment my neurologist advised that we should consider this treatment a success if it was able to stop the progress of my Pompe disease, which was advancing quickly.

Before I started treatment, I was struggling to walk more than 10m and just getting around our house was a challenge. To help us gauge the success of the treatment my neurologist recommended I have an MRI scan of my lumbar spine before starting treatment, which I have continued on an annual basis since.

After about six months of fortnightly infusions known as Enzyme Replacement Therapy treatment I noticed the progress of the disease had stopped and I regained a little of the strength I had lost. Over time I was able to improve my walking. With some assistance I was able to walk 36m. Follow-up MRI scans confirmed the progression had stopped.

Now in 2013, six years later, I am still able to walk around the house but if I venture further I use a wheelchair. I have a family history of Pompe, having lost my brother who after many years of increasing disability, the last two years in intensive care, passed away at the age of 54. Unfortunately my brother never had the opportunity of treatment as he was diagnosed long before treatment was available.

I am the president of the Australian Pompe's Association. I hope that with improving diagnosis and treatment we can find a cure for Pompe disease and save other families from this experience.

The Australian Pompe's Association
www.australianpompe.com

Source: 'The Australian Experience of Living with a Rare Disease' Megan Fookes, 2014, Rare Voices Australia Ltd. Available at: http://rva.blob.core.windows.net/assets/uploads/files/RVA%20Experience-48pp-PDF.pdf

In 2013-14

the Australian Government spent **less than 0.21% of the health budget on rare disease therapies under the LSDP.**[11]
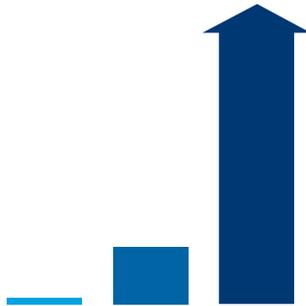
EXPENDITURE ON RARE DISEASE THERAPIES UNDER THE LSDP OF

$80 million[12] is a tiny fraction of the

$10.3 billion the Australian Government spent on pharmaceutical reimbursement and the

$64.6 billion spent on health generally.[13]

Growth in funding of specialised rare disease therapies under the LSDP has been miniscule, making it a manageable component of the health program. Funding new therapies for rare conditions under the LSDP represents just 0.24% of the anticipated growth in health expenditure between 2013-14 and 2017-18.[14]

Rare disease treatments funded under the HSDP are similarly small relative to the total PBS budget, though a breakdown of costs for rare disease therapies is not publicly available.

While Australia lacks a single definition for rare diseases, the Therapeutic Good Act definition for registration of an orphan drug applies a far tighter definition to rare disease that comparative countries – less than 2000 patients or the equivalent of 1 in 10,000 persons – thus limiting access to medications relative to comparable countries.

In South Korea a rare disease is one diagnosed in less than 1 in 2,500 persons[15]; in Canada[16] and the EU[17] it is less than 1 in 2000 persons; in the US it's one in 1,500.[18]

4. An Ethical Framework for Funding Rare Disease Therapies

In this report, we argue that rare diseases are significantly different to more common diseases, and that a fit for purpose mechanism is needed for allocating resources to those with rare diseases.

The arguments in this report take two main forms: 1) economic arguments, focused on the pros and cons of different models for allocating scarce resources, and 2) arguments based on community and patient values.

At their core, both of these kinds of arguments are about what we as a society value the most. They are, therefore, fundamentally about "ethics".

In this section, we will briefly describe the ethical arguments for and against a fit for purpose process for rare disease therapies, with a focus on different understandings of "distributive justice", i.e. different ideas about how to distribute healthcare benefits in an ethically sound manner.

Ethical arguments in favour of a fit-for-purpose process for rare disease therapies

Those who argue for a fit-for-purpose rare disease process are concerned not only about maximising healthcare benefits for the population as a whole (known as horizontal equity), they are concerned about addressing unjust inequalities (known as vertical equity).

In the case of rare diseases, the relevant inequality is that people with rare diseases are less able

than others to obtain the resources they need. Specifically, the combination of small clinical trials and expensive medicines (in terms of unit costs) make it almost impossible to demonstrate that medicines for rare diseases are "cost-effective" at a population level.

There is therefore little, if any, chance that they will be funded on schemes such as the PBS. This is unjust because it entrenches, rather than reduces, inequality.[19]

However, cost-effectiveness is only one possible justification for the funding of medicines. Those in favour of a fit-for-purpose mechanism for rare diseases also note that there are a number of other possible moral justifications for funding, which are not considered systematically in mainstream funding processes.

Other justifications include but are not limited to: 1) vertical equity itself (reducing inequalities simply because they matter and because we can afford to do so), 2) compassion, 3) protection of the vulnerable, and 4) rescuing of those in dire need (the "rule of rescue").[20]

Given that these justifications are likely to be particularly salient when it comes to rare diseases, it follows that a process suited to rare diseases is

needed that is able to systematically and explicitly consider these justifications alongside other considerations.

Furthermore, those who argue for a fit-for-purpose mechanism for rare diseases note that standard measures of cost-effectiveness tend to be based on a relatively narrow understanding of "effectiveness," with an emphasis on parameters such as longer lifespan, improved quality of life (according to pre-defined criteria), and reduced costs to the health system.

Less attention is paid to the broader value of medicines including factors such as reduced carer burden, "holistic" care, and predictable returns to the pharmaceutical industry so that it will continue to invest in developing needed medicines. These factors are all known to be important to patients with rare diseases, their clinicians and their carers,[21] so it makes sense to ensure a fit-for purpose process exists for rare disease therapies that can systematically broaden the notion of healthcare benefits to include these other factors.

Ethical arguments against a fit for purposes process for rare disease therapies

Those who argue against a fit for purpose process for rare disease therapies base their argument on the importance of maximising healthcare benefits for the population as a whole. Their notion of distributive justice, sometimes also called horizontal equity, is therefore a utilitarian one, aiming for the "greatest good for the greatest number," rather than one focused on reducing unjust inequalities.

The concern that people with this understanding of justice have about programs that apply specific criteria to rare diseases is that they divert resources towards a small subset of the population, to the detriment of the population as a whole. With a limited healthcare budget, the use of any resources for one purpose, such as rare diseases, inevitably creates an opportunity cost and reduces what is available to others.[22]

Those with concerns about the cost of rare disease therapies also note that softening evidence requirements in order to facilitate access is not always to patients' advantage. All medicines – including medicines for rare diseases – can prove to be less effective than originally believed, and can have unexpected adverse effects. Patients with rare diseases might, therefore, be harmed if medicines are funded without clear evidence of efficacy and safety.[23]

People who take this view are, therefore, generally supportive of the current guiding principles for funding on the PBS, which emphasise the need to demonstrate clear evidence of efficacy, safety and population level cost-effectiveness in order to justify funding.
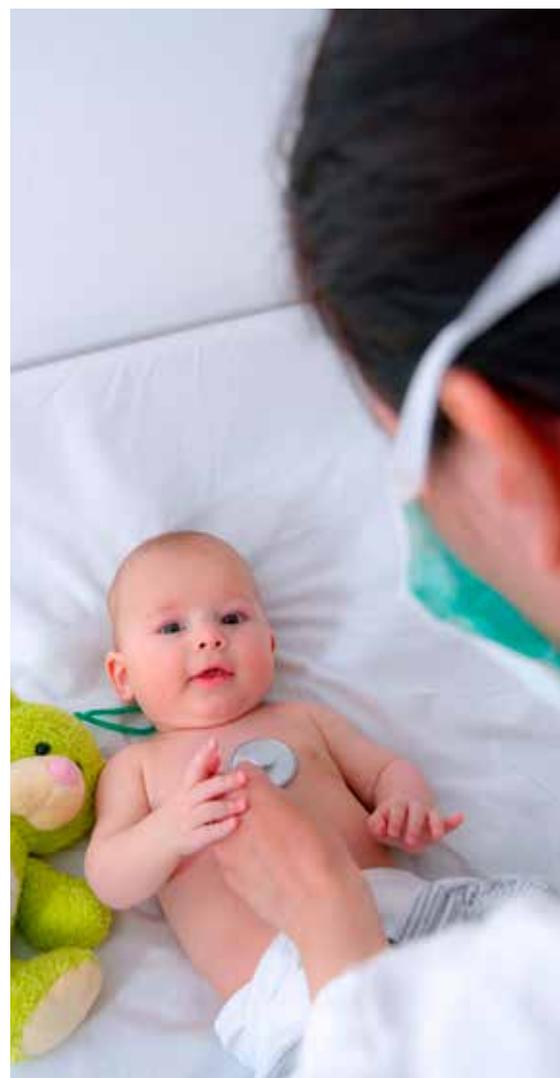
The need for explicit ethical compromise and attention to procedural values

It is important to note that both "sides" of the argument are concerned about the same broad ethical principle: that of "distributive justice".

The difference between the two positions is not that one is "ethical" and the other is "unethical". Rather, each has a different understanding of what it means to distribute healthcare benefits in a "fair" or "just" manner, and different ideas about what these benefits actually are, and how they should be prioritised [Figures 1 and 2].

FIGURE 1:
ELEMENTS OF DISTRIBUTIVE JUSTICE

LONGER SURVIVAL

ENHANCED QUALITY OF LIFE

HOLISTIC CARE

DEMONSTRATED EFFICACY AND SAFETY

REDUCED HEALTH SYSTEM COSTS
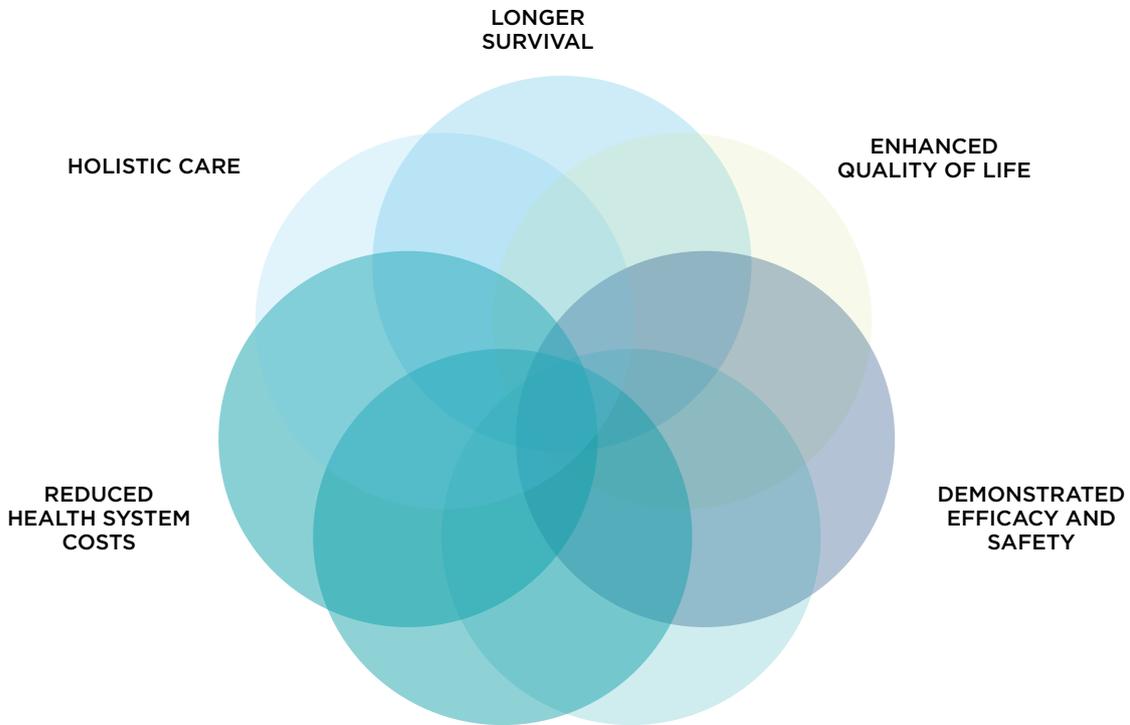
FIGURE 2:
VARYING IDEAS ABOUT THE GOALS OF HEALTHCARE FUNDING

DISTRIBUTIVE JUSTICE

HORIZONTAL EQUITY

VERTICAL EQUITY
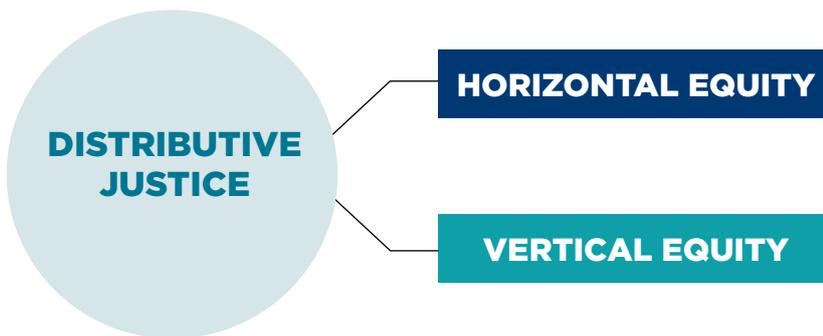
While the various notions of justice and the different goals of funding clearly intersect, they do not overlap completely, and achievement of one goal or set of goals may challenge fulfillment of others.

Furthermore, ideas about justice and healthcare benefits are culturally shaped, and different individuals and groups will inevitably understand and express them in different ways. On the basis of what we know about public attitudes, it seems likely that members of the Australian community would value both population-level cost-effectiveness and the resolution of unjust inequality.[24]

Any approach to the management of rare diseases therefore needs to be explicit about the values it privileges, those it sets aside, and how these compromises will be accommodated.

It also needs to satisfy a number of "procedural" values, such as accountability, integrity, transparency, inclusiveness and timeliness [Figure 3].[25] Processes that reflect procedural values contribute to both the perception and realisation of outcomes that are considered to be more inclusive. Applying the procedural outcomes outlined below can contribute to the achievement of outcomes that can be more clearly understood and potentially accepted by stakeholders.

FIGURE 3: PROCEDURAL VALUES

ACCOUNTABILITY

INFORMED & NUANCED DECISION-MAKING

TRANSPARENCY

INTEGRITY

TIMELINESS

COORDINATION & HARMONISATION

TRUSTWORTHINESS
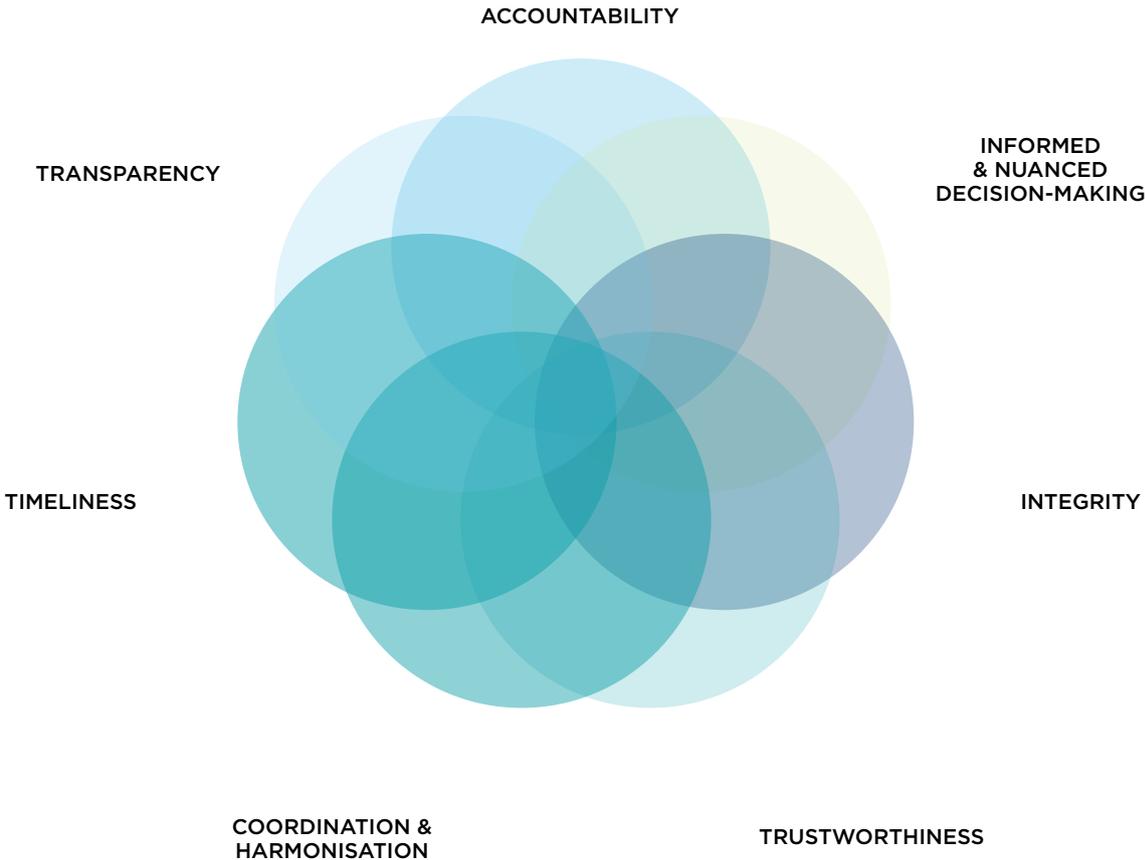
- **OBJECTIVITY** refers to the ability to manage one's personal interests when making decisions. It should be assumed that everyone involved in decision-making has interests (financial or otherwise) that might sway their decisions. A sufficient degree of objectivity can, however, be maintained through declaration and active management of these interests.

- **INCLUSIVENESS** refers to involvement in decision-making of all relevant stakeholders. In the context of funding for rare diseases, these stakeholders might include patients, lay carers, patient advocates, clinicians, the pharmaceutical industry, Government, and taxpayers.

- **TIMELINESS** refers to the speed of decision-making processes. For example, it might be important to coordinate regulatory decision-making and funding decisions so that access is not delayed unnecessarily, and to harmonise decision-making processes across jurisdictions.

- **ACCOUNTABILITY** refers in this context to acknowledgment and assumption of responsibility for actions, decisions, policies and products. It also implies an obligation to report, explain and be responsible for the outcomes of the above. It is, therefore, closely related to transparency.

- Finally, **INFORMED AND NUANCED DECISION-MAKING** refers to the principles according to which decisions are made. Processes such as Multi-Criteria Decision Analysis (MCDA), which incorporate numerous decision criteria and also allow for weighted consideration of the criteria, have been developed in an effort to achieve this goal.

When these procedural values are adhered to, then trustworthiness is maximised. Trustworthiness refers to behaviour that instills in external stakeholders the belief that decision-makers have their interests at heart, and, where full participation and transparency are not possible, can be left unsupervised to serve these interests. This, in turn, creates a sense among stakeholders that decisions are *legitimate*, even if not everyone can be satisfied by a particular outcome.

As with the other values illustrated above, procedural values will inevitably be understood and prioritised differently by different stakeholders. For example, people often disagree about who should represent the "consumer" voice in decision-making and how these consumers should be engaged.[26] Similarly, industry may have more concerns than other stakeholders about protecting commercially confidential information and may, therefore, have different ideas about transparency.

An overarching ethical framework

On balance, the ethical arguments in favour of having a fit for purposes process for rare disease therapies are stronger than those against it. This case is made further throughout this report.

We acknowledge that the approach we recommend places more importance on vertical equity than on horizontal equity, and that this could potentially lead to problems if the scheme is used unwisely.

We try to accommodate this by recommending clear parameters for a fit for purposes process for rare diseases, and by focusing on a number of procedural values such as accountability, transparency, integrity and trustworthiness, coordination and harmonisation, timeliness, and informed and nuanced decision-making [Figure 3].

The proposed approach is ethically justifiable and best suited to accommodating and balancing myriad social values that are at stake in the management of rare disease therapies.

5. Australian Context

Australia's Pharmaceutical Benefits Scheme (PBS) is arguably at the forefront internationally of using health technology assessment (HTA) to evaluate medicines for funding.

Australia's system seeks to balance the principles of cost effectiveness, equity and universality. However, the principles underpinning the PBS do not adequately deal with drugs for rare and life threatening conditions, which affect a small proportion of the population.

In Australia there is no single definition of a rare disease. The Therapeutic Goods Act does contain a definition of an orphan drug for the purposes of registration as one that has fewer than 2000 patients. This is approximated as the equivalent of 1 patient in 10,000 persons.[27] If applied as the

closest available rare disease definition in Australia, this is a far narrower definition of rare disease when compared to comparable countries (Table 1).

It can take 10 to 12 years and $2 billion to develop and bring a new therapy to the market.[33] Because these costs are not directly related to the number of potential patients, the per-patient costs of therapies for rare diseases are much higher than therapies for more common diseases with larger patient populations.

TABLE 1: DEFINITIONS OF RARE DISEASE

WHAT IS A RARE DISEASE? DEFINITIONS VARY AROUND THE WORLD.	
Australia[28]	**<1 in 10,000 persons**
United States[29]	**<1in 1,500 persons**
Canada[30]	**<1 in 2,000 persons**
European Union[31]	**<1 in 2,000 persons**
South Korea[32]	**<1 in 2,500 persons**

THE UNCERTAINTY OF LIVING WITH A RARE DISEASE

Individuals living with a rare disease face many obstacles and challenges in addition to living with the symptoms and long term prognosis of their disease.

First, there is uncertainty from delays in getting a correct diagnosis due to a lack of specialty care and inadequate use of technology.

A survey in the UK found that on average it takes 5.6 years and 2 to 3 misdiagnoses before a patient with a rare disease receives a proper diagnosis.[34]

Even after a correct diagnosis there is often not an available treatment or cure, making the future uncertain and dependent on a medical breakthrough.

For those for whom a treatment or cure is or becomes available there is further uncertainty as therapies are often prohibitively expensive and there is no guarantee that public or private insurers will fund them.

As a result, new drugs for rare diseases are generally unable to meet standard PBS cost-effectiveness criteria, as the unit cost of therapies is too high.

While the PBS does take into account rarity of the disease and the rule of rescue (the moral and psychological imperative to rescue those in dire need) when setting the threshold, the cost of some new therapies for rare diseases mean that they will never meet the threshold.

For example, some new treatments for chronic and life shortening rare conditions can cost in the order of $300,000 a year for life,[35] raising questions regarding cost effectiveness, efficiency and horizontal equity, discussed above in the ethical framework. These treatments will never meet standard cost-effectiveness thresholds and be funded under the PBS.

The catastrophic nature of many rare diseases also means that the impact on the families and carers of sufferers is high compared to many other diseases. These impacts are not explicitly factored into the standard cost-effectiveness considerations of the Pharmaceutical Benefits Advisory Committee (PBAC), underestimating the potential benefits of new therapies for rare conditions.

The lack of funding for therapies for rare conditions presents a number of policy issues:

- Individuals are denied access to lifesaving or life changing therapies that are deemed not cost-effective because insufficient people have the same condition, thus creating and entrenching vertical inequity.

- Greater strain is placed on our health and community care services to provide support for people suffering from rare diseases who are unable to access existing therapies or benefit from new therapies being discovered due to lack of funding.

- The medicines industry is discouraged from researching and developing new therapies, reducing the effectiveness of policies to encourage such research, and the prospect of cures and treatments of rare conditions.

■ Potential innovation spillovers from rare disease research into more common conditions are not realised, removing an important potential source of cost savings for the health system into the future.

Recognising these issues, the LSDP program was established in the mid 1990s to provide people suffering rare and life threatening diseases access to drugs that did not meet the standard PBS criteria. This program, named the Live Saving Drugs Program, provided an avenue for therapies for rare and life threatening diseases to be funded under Australia's universal healthcare system.

Since then, the program has funded therapies primarily for rare enzyme disorders.

The program was reviewed in 2010,[36] leading to a significant tightening of access to funding for new therapies and reduced transparency, leading to many of the current issues, discussed further in the following section. It is now being reviewed for a second time.

The review is welcomed by rare disease patients, their families, health experts and industry. It is an important opportunity to consider the future funding of rare disease medications and ensure Australians are receiving the care they need.

It is important that this review be undertaken in consultation with clinicians, patients, the pharmaceutical industry and state governments to ensure the challenges that persist for rare disease patients and industry are met.

In undertaking the review patients and the medical research and pharmaceutical industry are looking to government to build confidence in the process for rare disease therapies, critical to ensuring investment in research and treatment continues.

The review would also benefit from considering the path that many people with rare diseases must travel, from delays in receiving an initial diagnosis, to limited treatment options and meeting long term care needs.

A whole of Government strategy covering diagnostic services, accessing and funding existing, new and experimental therapies and meeting long term care services would ensure that Australia is well placed to deal with rare disease management challenges today and into the future.[37]

BRINGING A NEW THERAPY FOR A RARE DISEASES TO MARKET

Bringing a new therapy to market involves three distinct stages:

1. Discovery and Development
2. Registration and Marketing Authorisation
3. Patient Access to Medicines

In each of these stages, specific challenges exist in the case of new therapies for rare diseases.

These add to the cost and uncertainty of developing new therapies. Addressing these issues through better regulatory practices will help ensure that more new therapies become available in the future.

DISCOVERY AND DEVELOPMENT

Research and development is more complex and time consuming due to the nature of rare diseases.

By definition there are a small number of patients, and many rare diseases frequently present with a wide variety of different clinical symptoms, making identification difficult.

Limited prior research means that the biology of these diseases is poorly understood, limiting the ability to use animal or computer models in research. This reduces the ability to fully utilise prior research in the discovery phase.

Once identified, developing a product through clinical trials is further complicated by small numbers of research participants, geographical spread and an under-diagnosed or mis-diagnosed patient population. In addition, having a placebo controlled arm in a clinical trial creates a significant ethical issue where there are no other treatment options available to patients.

These issues mean that gold standard clinical trial designs are often not feasible, creating issues on the acceptability of data from trials, which often differ across jurisdictions.

REGISTRATION AND MARKETING AUTHORISATION

Assessing new therapies for rare diseases is a complex process that requires highly specialised expertise, both in the disease and in the assessment processes, which regulators may lack.

The need to assess data from non-standard trials and the difficulty in determining the best approach for patients who will benefit from a new treatment often delay final decisions by regulators.

PRICING AND REIMBURSEMENT

Many countries have augmented their conventional HTA systems to deal with therapies for rare diseases. While these alternate approaches attempt to address the special nature of therapies for rare diseases, they create a myriad of systems for companies to traverse globally.

Even when approved for funding, patient access to therapies is often limited and complicated through prescription restrictions. This may require not only specialist prescription but ongoing evaluation of individual patient responses to therapies.

Companies are often required to set up registries and conduct post approval studies to fulfil regulatory requirements. While these registries are important and useful, the different requirements across jurisdictions add to costs and uncertainty.

Case Study

JORDAN AND LOGAN'S STORY

LIVING WITH CHRONIC IDIOPATHIC INTESTINAL PSEUDO OBSTRUCTION LINKED FILAMIN A DEFECT, NSW

Chris Walker, a proud grandfather fondly called 'Pop', talks about supporting his grandsons who live with a very rare condition..

"As a hard-working Australian of Scottish heritage, I come from a family that has contributed to Australian life through exploration, the arts, sport and in many other ways. There have been stories of great success and also of rotten luck.

It was my interest in genealogy that led me to the diagnosis and understanding of the very rare disease that has affected my grandson Jordan, who is now four years old. He spent his first 14 months in hospital.

This very rare genetic disease we discovered was called chronic idiopathic intestinal pseudo obstruction linked filamin a defect, which is usually fatal and found in males. Research into family history found other similarly-affected males. I had to resort to putting the family tree above Jordan's bed to get the doctors to pay attention to our family history. Even when we had a diagnosis for Jordan, we were unable to prevent another child being born with the same condition, as Logan's mother was already pregnant by the time we found out. It was only when a medical student noticed our family tree on a hospital notice board that we finally got offered genetic testing. To this day, the two sets of medical teams in two different states have not spoken to each other.

This disease can't be fixed, just treated, and requires constant care. For Jordan, this means tubes to drain fluids from the small intestine from both sides of his abdomen and a naso-gastric tube hooked to a pump for fluid replacement. Causal vomiting is also part of the problem, along with the health system's inability to be able to deal with the requirements of providing support to those caring for Jordan and Logan, who is much more severely affected. Caring for the boys in their own home involve most family members, with all of the additional costs being borne by the family as a whole. Both boys will require Total Parenteral Nutrition for life, as well other surgeries.

The two boys simply don't fit the boxes of an inflexible funding system.

We know that the National Disability Insurance Scheme is a magnificent development, but I honestly don't think we can survive until 2018 (as officially advised) without help. We were paying in the vicinity of $200-$500/week for medical supplies and medications. Until recently we received no support at all, because even charities which claim to be flexible have very strict guidelines and we just don't fit.

Without the wonderful support of the likes of a number of charities in recent months we were wondering how much longer we could go on. There was no support from either State or Federal governments to provide the air-conditioning for the boys, who are unable to regulate their body temperature.

A charity stepped up and helped us with that. We have also been able to access support from other charities as well, with case management and funding to help with the cost of the dressings and medications. We are extremely grateful to them but it is not good enough that a family has to run a virtual hospital ward at home, without the help that is given to high profile diseases.

Surely as Australians we can do better than this for those so affected by such rotten bad luck!"

Source: 'The Australian Experience of Living with a Rare Disease' Megan Fookes, 2014, Rare Voices Australia Ltd. Available at: http://rva.blob.core.windows.net/assets/uploads/files/RVA%20Experience-48pp-PDF.pdf

6. International Context

Australia is not alone in grappling with the issues raised by therapies for rare diseases.

The growth in the number of identifiable rare diseases and available treatments has presented governments worldwide with significant challenges that have been heightened by the constrained post-GFC budget environment.

International responses provide some guidance on potential approaches that might be adopted by the Australian Government. While approaches vary, almost every government has applied special criteria and processes for therapies for rare diseases reflecting an understanding that they are fundamentally different to other diseases.

An analysis of approval processes for rare disease therapies against comparable countries (Table 2) indicates that Australians are not only being denied therapies made available in other countries, but are also waiting much longer for access when granted.

Based on an available sample of approvals for select drugs over the last 4 years, **Australians are generally waiting anywhere from 2 – 4 years longer for access to government funded treatments for rare diseases than in comparable countries (Table 2). Some medications remain unavailable 8 years after becoming available overseas.** For some rare disease therapies available overseas, access may never be granted in Australia without policy reform.

While this delay reflects a range of factors, including the timing of patient trials, applications for approval for funding in Australia, and a relatively small number of therapies, the delay in access demonstrates the uncertainty for patients, clinicians and the sector in the provision of rare disease therapies in Australia.

This is indicative of a system that needs reform to streamline the assessment process and provide Australians with timely access to life saving and life changing therapies, that they could access months or even years sooner if they lived in other countries.

In this section we look at the approaches taken in five comparable settings: Germany, Netherlands, the UK, Ontario Canada and South Korea. We then analyse how these different approaches have treated each of the new therapies considered under the LSDP since the Australian 2010 reforms.

While the international comparison reveals diverse systems for managing and funding rare disease therapies, the evidence increasingly points to the need for a consultative process with industry, clinicians and patients, as well as assessing multiple criteria to ensure the unique elements of rare diseases are at the forefront of decisions about the funding and approval of rare disease therapies.

Governments worldwide are increasingly aware of the inequity faced by rare disease patients where access to therapies are denied and of the challenge this presents to managing health costs, medical research and development, and equitable access to health services for all citizens.

Governments across the world have undertaken various reviews, discussed below, and systems are being designed that better meet the challenge of funding rare disease therapies and better valuing those treatments. In undertaking the current review, Australia is well placed to draw on international experience to ensure Australian patients have access to world leading rare disease therapies.

TABLE 2: SAMPLE OF APPROVALS FOR SELECT DRUGS

Drug	Brand Name	Manufacturer	Indication	Australia	England	Ontario Canada	Netherlands	Germany
Miglustat	Zavesca	Actelion Pharmaceuticals Australia	Niemann-Pick type C Disease	Not Available	July 2009	Nov 2010	2009	2009
Alglucosidase alfa	Myozyme	Genzyme Australia – A Sanofi Company	Late onset Pompe disease	Not Available	May 2006	June 2009	2006	2006
Velaglucerase alfa, powder for IV infusion	Vpriv®	Shire Australia	Type 1 Gaucher disease	March 2012		Dec 2010	2010	2010
Taliglucerase alfa	Elelyso	Pfizer Australia	Type 1 Gaucher disease	Not Available	Rejected*		Rejected*	Rejected*
Eculizumab	Soliris	Alexion Pharmaceuticals	Paroxysmal nocturnal haemoglobinuria	June 2012	April 2009	July 2010	2007	2007
Eculizumab	Soliris	Alexion Pharmaceuticals	Atypical Haemolytic Uraemic Syndrome	Dec 2014	August 2013		2011	2011
Sapropterin	Kuvan	Merck Serono	Hyperphenylaninanemia	Nov 2012		April 2010	2008	2008
Ivacaftor	Kalydeco	Vertex Pharmaceuticals	Cystic Fibrosis	Dec 2014	Dec 2012	June 2014		August 2012

Vpriv granted exclusive access for 10 years

NOTE: *Limited data is available on the timing and listing of rare disease medications across jurisdictions. The above information has been collected from publicly available sources and in some cases pharmaceutical companies have provided data for their respective rare disease therapies in each jurisdiction.*

The German approach

The German government introduced wholesale reforms to its system of therapy reimbursement in 2011 with the *Pharmaceutical Market Restructuring Act*.[38]

Prior to the Act all new therapies were only required to be clinically effective to be funded. There was no requirement that there be a net benefit compared to an existing therapy from the new therapy, and companies could charge any price for a new drug. This is a very different approach to that applied in Australia.

The 2011 reforms introduced a tougher system of reimbursement and aimed to lower the growth in costs of pharmaceuticals and ensure that therapies funded were providing additional benefit.

Under the new system therapies must demonstrate an additional benefit to existing drugs or be deemed equivalent to an existing drug and be subject to reference pricing.[39]

However, the reforms exempted orphan drugs which are defined as therapies with sales revenue of less than 50 million Euros.

As a result, under the German system all orphan therapies designated by the European Commission are funded, as long as their total annual cost is less than 50 million Euros.[40]

This relatively straightforward approach attempts to strike a balance between providing patients with access to therapies for rare conditions, and ensuring budget sustainability.

The Dutch approach

On 1 January 2014 the Netherlands introduced reforms to its access and funding arrangements for therapies for rare diseases.[41]

Historically, therapies for rare diseases were funded through the Medicines Reimbursement System or the hospital setting.

However, all orphan therapies authorised by the European Community are now reimbursed through a hospital setting.

The reforms are part of a broader policy to transfer the provision of all specialist therapies to the hospital setting.

If a physician prescribes an orphan therapy, hospitals are reimbursed via an add-on to the standard funding for the treatment of the rare disease.

95 per cent of the cost of the therapies on the list is reimbursed by the Ministry of Health, with the remaining 5 per cent being paid from the hospital budget.

This new approach is also being applied to patients with common conditions, such as arthritis, for whom specialised medicines have been developed. Specialised medicines may treat a specific stage of a disease or be administered because individual patients have not responded to standard therapies.

The Dutch approach removes reimbursement decisions for therapies for rare diseases and specialised therapies completely from the mainstream evaluation approach.

Instead, specialist physicians treating individual patients have the discretion to administer such therapies where they deem it clinically necessary and appropriate.

Such an approach recognises that standard reimbursement approaches are not appropriate for therapies treating rare conditions. It ensures that all patients deemed by specialised physicians as able to benefit from a rare therapy have access to such therapies.

This approach reduces central government control over the scale of spending on therapies for rare conditions. However, the inclusion of cost sharing with hospitals alleviates some of these concerns.

The Dutch system also has ability to revisit data over time, as was seen with Fabry and Pompe disease therapies in 2013.

The English and Welsh approach

The National Institute for Health and Clinical Excellence (NICE) evaluates new therapies in England and Wales. Since 2002, it has been mandatory for all National Health Services in England and Wales to fund therapies recommended by NICE.

Similar to PBAC in Australia, NICE evaluates the cost-effectiveness of new therapies using HTA.

NICE's standard process considers the rarity of the disease being treated and availability of alternatives when setting an acceptable cost per quality adjusted life-year (QALY) threshold. For example, a higher threshold may be set reflecting the rare nature of the condition that the new therapy treats. Notwithstanding this, many treatments for ultra-rare diseases generally do not meet even these higher thresholds due to unit cost.

Previously, therapies for ultra-rare diseases affecting less than 1 per 50,000 population were considered by a separate specialist body, the Advisory Group for National Specialised Services (AGNSS), however these recommendations were not binding and were frequently ignored.[42]

In April 2013, responsibility for ultra-orphan therapies was transferred to NICE and a separate process was established.

In its interim guidance, NICE has implemented Multi-Criteria Decision Analysis (MCDA) in its HTA assessment of ultra-orphan drugs, to include criteria beyond cost-effectiveness. Rather than an automatic cut off for cost-effectiveness based on cost per QALY, cost-effectiveness is considered alongside other factors.

While similar to the approach taken by the LSDP, the MCDA appears to provide a more rational, rigorous, fair and transparent framework.[43]

For example, NICE considers a wider set of factors when undertaking HTA assessments of ultra-orphan drugs:[44]

- Impact of the disease on carers' quality of life.

- Overall magnitude of health benefits to patients and, when relevant, carers.

- Whether there are significant benefits other than health, including whether a substantial proportion of the costs or benefits are incurred outside the NHS and personal and social services.

- The potential for long-term benefits to the NHS of research and innovation.

The process also allows for weighted consideration of the criteria, unlike the LSDP where all criteria must be fully met in order for a new therapy to be recommended for funding.

The NICE is currently undertaking a full consultation on the new framework for evaluating rare diseases. A key focus of UK industry groups is the need consistency in definition of orphan and ultra-orphan diseases to better align with international standards and ensure greater access to treatment for rare diseases.[45]

The Canadian approach

There are systems operating in Canada, one at the national level but administered by the Provinces, and a separate system that operates in the state of Ontario.

NATIONAL APPROACH

Similar to NICE and PBAC, the Canadian Agency for Drugs and Technologies in Health (CADTH) uses a cost-effectiveness framework to make recommendations on the funding of new therapies under its Common Drug Review (CDR) process.

In May 2014 a review of the process for funding new treatments for rare diseases concluded that no separate process would be established. Instead minor adjustments for rare diseases are being considered to the current CDR process.[46]

Under the current system, when CADTH makes a determination about cost-effectiveness of a new therapy under the Common Drug Review process, individual provinces and territories decide whether to fund these therapies.

Some jurisdictions have special criteria for rare therapies (see detail on Ontario's approach below) while others apply strict cost-effectiveness criteria. This creates geographical inequity across Canada with access to certain therapies contingent on where you live.

The Canadian Government is currently developing a broader orphan drug framework for the first time.

The framework will cover the determination of an orphan therapy, and its authorisation and monitoring. It aims to provide faster access to therapies for rare diseases and encourage research and innovation in Canada.

ONTARIO

Ontario introduced a draft Drugs for Rare Diseases (DRD) Framework in 2010.[47] It aims to influence the development of the national framework with its experience.

The DRD framework comprises six steps:

STEP 1: Determine whether the disease is rare

STEP 2: Review the natural history of the disease

STEP 3: Assess the potential effectiveness of the treatment, using best available evidence

STEP 4: Evaluate total budget impact

STEP 5: Identify additional follow-up data required

STEP 6: Consider "social values" based on input of Ontario's Citizens

Importantly, while considered as part of the process, cost-effectiveness is not the sole deciding factor in funding new therapies. Instead, social values and benefits are considered alongside budget impact and effectiveness in funding decisions.

The South Korean Approach

South Korea is a middle-income country with a GDP per capita less than half that of Australia. Despite this, South Korea has a comprehensive rare diseases policy that helps ensure access to therapies for people suffering from rare conditions.

South Korea introduced reforms to the reimbursement of new drug therapies at the end of 2006, through the Health Care System Reform Act. It was the first Asian country to formally use economic evaluation in health resource allocation decisions.

The reforms introduced a positive list in response to rising health and pharmaceutical costs. Before the reforms South Korea operated a negative list and reimbursed over 20,000 therapies, this number has since been reduced to 13,000.[48]

Under a negative list, the presumption is towards reimbursement for therapies granted marketing approval by the regulatory body. Under a positive list a case must be made for reimbursement of therapies following approval of market access.

Similar to Australia's PBAC process, manufacturers in South Korea apply to the Health Insurance Assessment and Review service (HIRA) to have therapies reimbursed. HIRA applies standard health technology assessment processes, with manufacturers having to demonstrate both clinical usefulness and cost effectiveness.

However, not all new therapies have to go through this process. If a therapy satisfies the following criteria, collectively known as the 'rules of rescue', then the Department of Health automatically enters into price negotiation ahead of reimbursement:

- There are no alternatives;

- It is a life threatening disease;

- It is an orphan therapy; or

- There is an overall survival improvement.

The total value of production or importation of the therapy must also be less than US $5 million annually.

Orphan therapies in South Korea are designated where they treat a condition or disease with less than 20,000 patients, or approximately 1 in 2,500 people.

Lessons from overseas

A summary of the international systems considered in this review is provided in Table 3.

It illustrates that Australia's LSDP is one of the more stringent schemes internationally for assessment of funding of therapies for rare diseases. In particular the requirement that each of the eight criteria (discussed below) be met is out of step with international approaches utilising forms of HTA.

Table 2 above looked in more detail at the path of approval for new therapies since the 2010 reforms, and illustrates that Australians with rare diseases are not gaining the same access to life saving or life changing drugs as in other jurisdictions.

Even where Australians are getting access to new therapies they are often waiting months if not years longer than in comparable countries.

For people living with a rare disease, such delays are difficult, and while many have been able to rely on compassionate access from pharmaceutical companies while submissions for funding are considered, such access is not guaranteed to continue into the future. Others are missing out even on access to compassionate programs.

Reforms are therefore needed to put Australians suffering rare conditions on the same footing as those suffering the same conditions overseas, and as Australians with more prevalent diseases.

TABLE 3: INTERNATIONAL SYSTEMS COMPARED

	Basis of Reimbursement of Therapies for Rare Conditions	Threshold for Special Consideration of Reimbursement for Therapies of Rare Conditions	Process for Special Consideration	Access to Approved Therapy	Adherence to principles of cost-effectiveness	Adherence to Rule of Rescue
Australia	Rule of rescue	Rejection by PBAC for listing on PBS Designation by TGA as an Orphan Therapy	PBAC assessment of whether new therapy meets each of 8 criteria for funding	Special conditions for initial access and ongoing access	No	Yes
Germany	Reasonable society cost of provision	Designated Orphan Therapy by European Commission; and <50 million euro annual cost	Automatic	Through social health insurers	No	Yes
Netherlands	Clinically determined need	Designated Orphan Therapy by European Commission	Automatic	Through hospital setting only	No	Yes
England	Multi-Criteria Decision Analysis	<1 patient in 100,000-150,000 population (Under review in the UK)	NICE using MCDA framework		Yes	Yes
Canada	Reasonable society cost of provision (reforms announced to include value for money)	NA	Special Cancer Fund	Applications must be made through cancer specialists	No (but reforms announced to include value for money going forward)	Yes
Ontario	Multi-Criteria Decision Analysis	<1 patient in 100,000-150,000 population	Drugs for Rare Diseases using MCDA framework		No, separate consideration of cost and effectiveness	Yes
South Korea	Reasonable society cost of provision	<20,000 patients <US$5 million annual import or manufacturing value	Automatic	Through Korean Orphan Drug Centre	No	Yes

7. Current and Future Challenges in Managing Rare Disease Therapies

Beyond the current policy and international comparisons there are a range of considerations that impact on the funding of rare disease therapies into the future. These challenges are considered further here.

Budget sustainability

The unit costs of new therapies for rare diseases are often high and alarming to potential funders; however these costs should be viewed in context.

In 2013-14 the Australian Government spent $80 million on the LSDP,[49] a small fraction of the $10.3 billion it spent on pharmaceutical reimbursement and the $64.5 billion spent on health generally [Figure 4].[50] This represents just 0.2% of total Commonwealth health spending.

Data on expenditure on rare disease therapies allocated under the PBS is not available for analysis.

GENERAL ADMINISTRATION
5.08%

LSDP
0.21%

ABORIGINAL & TORRES STRAIT ISLANDER HEALTH
1.24%

HEALTH SERVICES
10.60%

MEDICAL SERVICES & BENEFITS
40.91%

ASSISTANCE TO THE STATES FOR PUBLIC HOSPITALS
25.87%

PHARMACEUTICAL SERVICES & BENEFITS
16.09%
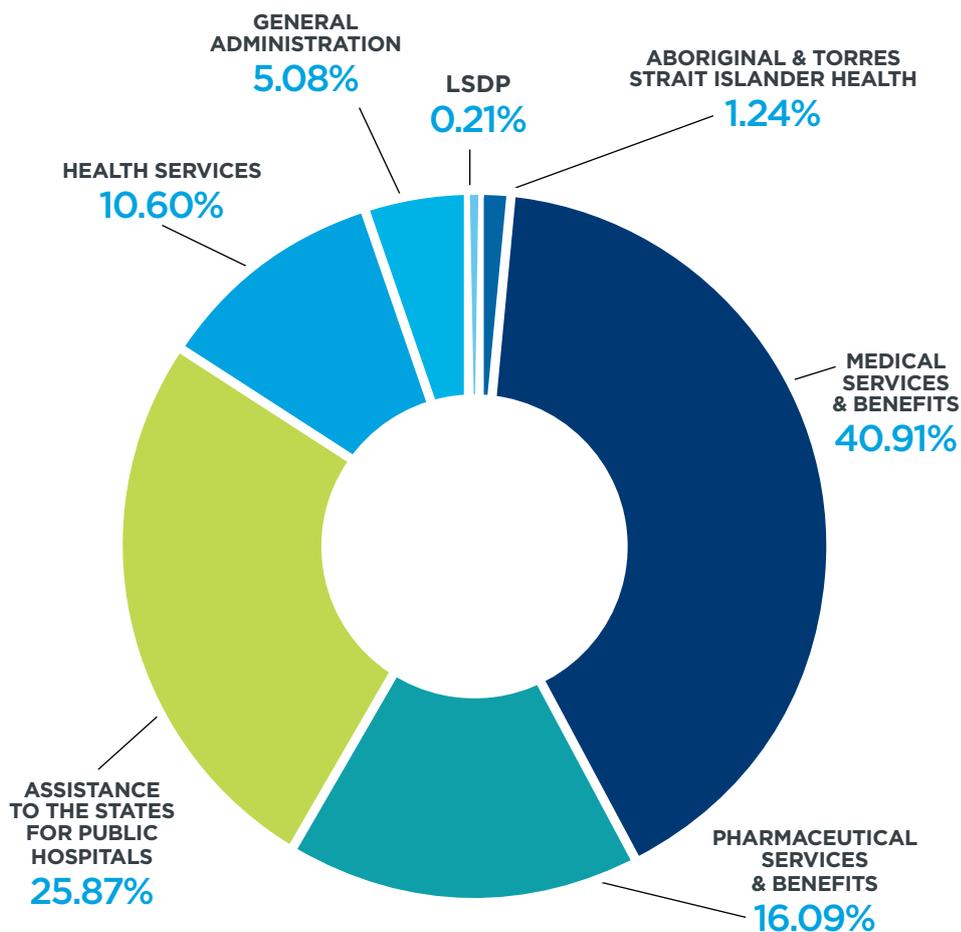
FIGURE 4: 2013-14 SHARES OF TOTAL COMMONWEALTH HEALTH SPENDING ($64.51 BILLION)

THE GROWTH IN
RARE DISEASE THERAPIES

At the start of 1980s there was widespread concern about the lack of new therapies reaching the market to treat rare and life threatening conditions.

In response, the United States led international reforms to encourage research and commercialisation of therapies for rare conditions with the *Orphan Drug Act 1983*.

Reforms included incentives for innovation, lower fees for approval applications, enhanced market exclusivity clauses and fast tracked assessments.

The reforms worked. In the 30 years after the Orphan Drugs Act was passed over 400 new therapies for rare conditions came onto the US market. This compares to just 10 therapies granted market access in the decade prior to its enactment.[51]

Other jurisdictions such as the EU followed, introducing policies to encourage the development of so called orphan therapies for rare diseases.

However, the success of the reforms in bringing new therapies to the market may well be their downfall.

Governments have been wary of the financial implications of funding new therapies.

As a result patients offered hope by the availability of new therapies to treat their rare conditions, have in many cases been denied access to those therapies due to Government reimbursement policies.

Manufacturers are now faced with a dilemma. Do they continue to develop new therapies for rare conditions in the absence of certainty around the funding of those therapies when they are brought to market?

Any potential additional cost of funding rare disease therapies needs to be viewed in the context of providing Australians with lifesaving and life changing treatments that they would otherwise not be able to access under standard PBS criteria.

While most therapies for rare conditions often do not meet standard cost-effectiveness criteria, they do provide some benefits to the budget that partially offset costs. These are in the form of reduced health expenditure including from reduced hospital admissions, reduced care and social security costs and increased economic activity due to reduction in disease related disability. These benefits are often overlooked and not consistently considered by the current process to determine the funding of new therapies.

Consideration should also be given to patent expiry for current therapies. The reduced costs associated with patent expiry will contribute to funding of the costs of new entrants, while ensuring greater access to rare disease therapies.

As recognised by the Government's proposed Medical Research Future Fund, new treatments for rare diseases have the capacity to reduce future budget pressures and the forecast growth in health and social care expenditure more broadly.

The relatively small cost of the LSDP and potential of rare disease therapies to partially offset costs are factors that need to be considered in terms of managing overall health expenditures. These considerations, combined with ethical considerations discussed above, make rare disease therapies an inappropriate area for cuts in expenditure.

Future challenges

In addition to addressing current policy issues with Australia's approach to funding therapies for rare diseases, reforms need to ensure that future policy challenges are also addressed.

The growing pressure from an ageing population will place significant pressure on Government health budgets and the capacity of the health system.

Finding new cures and treatments for diseases, including rare diseases, which are often accompanied by significant disability and high health and social care needs, will be an important part of the strategy to deal with an ageing population. This has been recognised by the Government's proposed Medical Research Future Fund.

Furthermore, the development of new highly personalised treatments for diseases presents challenges for policy makers in funding these

therapies. Different approaches are required to ensure that Australia fully benefits from these advances in treatment options and continues to be a world leader in providing access to new therapies.

Rising health care costs and an ageing population

The Government's Fourth Intergenerational Report, now likely to be released in 2015, is likely to again highlight the impact of an ageing population on health expenditure.

The National Commission of Audit, conducted in 2014, identified health expenditure as one of the Commonwealth's long running fiscal challenges [Figure 5].

Effectively managing growing health care costs is required to manage the long-term fiscal sustainability of the budget.

FIGURE 5: PROJECTED COMMONWEALTH HEALTH SPENDING (PER CENT OF GDP)[52]
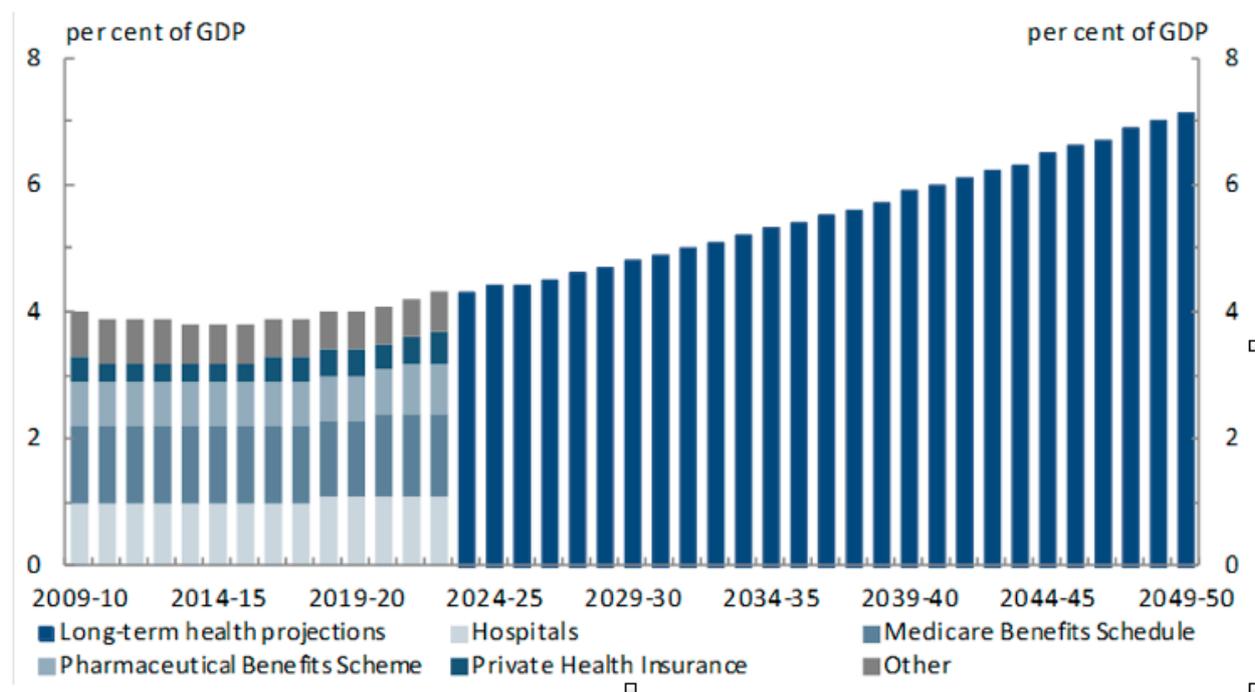
Funding new therapies for rare conditions under the current program will only marginally add to these costs, representing 0.24 per cent of the anticipated growth in health expenditure between 2013-14 and 2017-18 [Figure 6].[53]

Partially offsetting this growth however is the fact that new cost-effective therapies will increase the Government's ability to pay for rising costs more generally and reduce the pressure on the health system. Effective new therapies will help reduce caring needs, increase work force participation and improve overall wellbeing of individuals.

A narrow focus on the costs of new therapies ignores the benefits that can flow to the broader health system and the economy.

The policy framework needs to recognise the broader benefits from new therapies and the broader value of medicines, to ensure that by denying therapies for rare diseases funding we are not compounding the challenges associated with an ageing population.

Savings to indirect medical costs and productivity gains are not included in the current economic

evaluations undertaken to demonstrate cost-effectiveness to PBAC and would more accurately reflect the benefits of rare disease therapies.

The Government's proposed Medical Research Future Fund has recognised the need to fund research into new therapies for rare and life threatening conditions. The Government's announcement included that the Fund "… will facilitate Australia maintaining a world class medical research sector, with access to cutting edge innovation and clinical breakthroughs in our hospitals – the underpinnings of the health system of the future".[54] In doing so the Government has identified curing and treating rare conditions as an important element of containing future health care costs.

However, funding new therapies once they are developed is an important part of ensuring the ultimate effectiveness of such research.

Identifying and prioritising funding to provide certainty in access to those medical developments and innovation, particularly for rare disease patients, is needed to support that initiative.

FIGURE 6:
CONTRIBUTION TO GROWTH IN HEALTH SPENDING 2013-14 TO 2017-18

GENERAL ADMINISTRATION
0.25%

HEALTH SERVICES
1.94%

ABORIGINAL & TORRES STRAIT ISLANDER HEALTH
1.04%

ASSISTANCE TO THE STATES FOR PUBLIC HOSPITALS
37.58%

MEDICAL SERVICES & BENEFITS
48.84%

LSDP
0.24%

PHARMACEUTICAL SERVICES & BENEFITS
10.10%
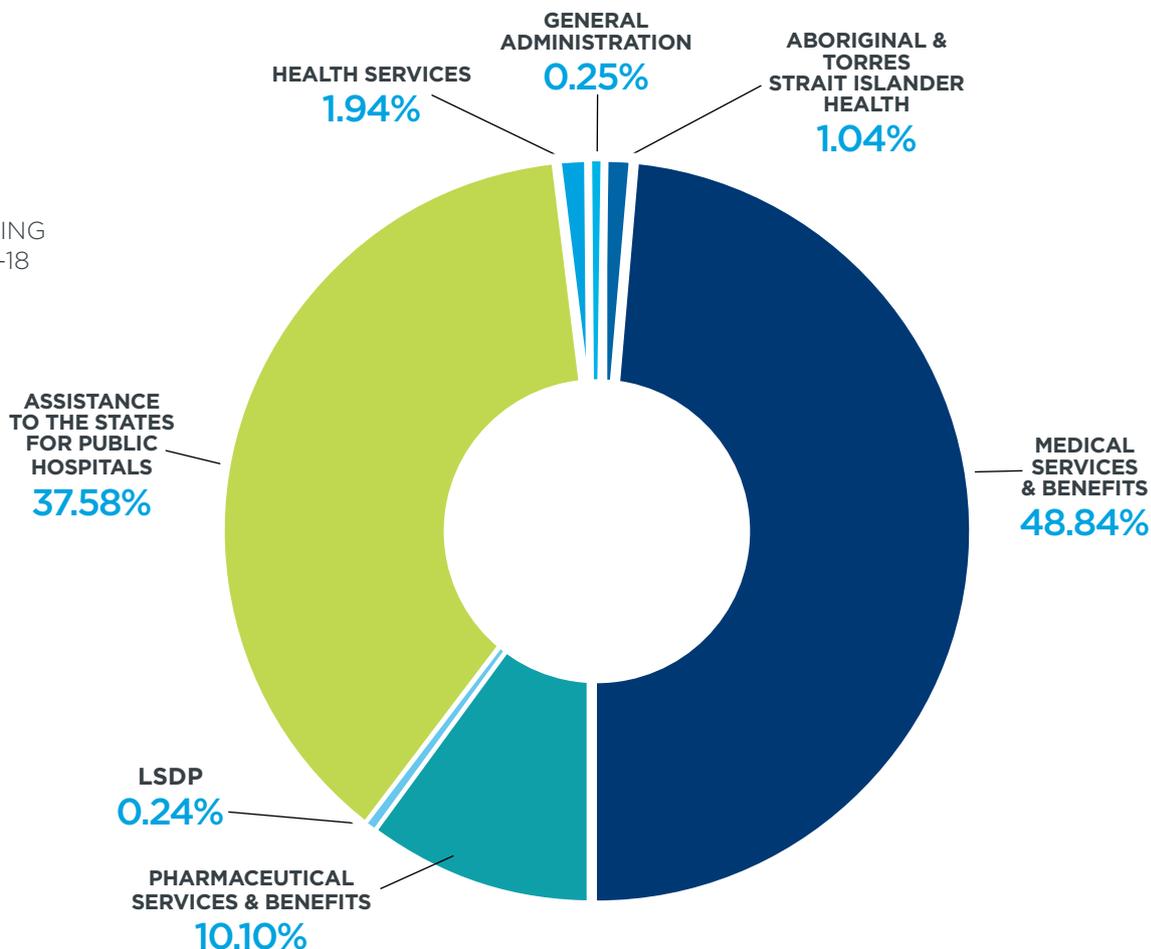
Genomics

Individuals are inherently unique and respond differently to different treatments. Following the mapping of the human genome in 2003, the possibility of being able to tailor treatments to the individual, delivering more certain and better outcomes with fewer side effects, has emerged.

Genomics or personalised medicines offer the prospect of revolutionising health treatment.

However, frustration is growing in industry and clinically at the inability of current processes in Australia and overseas to inform funding decisions for these new therapies.

There are inherent issues in determining the cost-effectiveness of treatments that are unique to the individual, presenting similar issues to those that arise in the assessment of rare diseases.

The Australian Government's 2009 Review of Health Technology Assessment recognised the difficulties of assessing personalised medicines for reimbursement decisions. This resulted in the Government providing improved coordination of applications requiring multiple HTA processes. However, it did not address some of the methodological issues with the current approaches.

For example, while running a standard randomised control trial to provide the evidence of effectiveness for a condition with hundreds of sufferers is difficult, doing so for a treatment specifically tailored to individual characteristics is impossible.

Data is required to support the effect of a biomarker on the treatment effect of a therapy to inform the decision to reimburse the test, the therapy, both or neither.

Research has been undertaken on the changes that would be needed to provide a feasible assessment framework.[55] There is a pressing need for Government to specifically consider these issues and develop a new approach for personalised medicines.

For example, consideration could be given to the joint assessment by a single body of the cost-effectiveness of the whole care pathway rather than separate consideration of each component. Not doing so will risk Australians missing out the significant benefit that genomics have to offer. The recommended National Strategy for Rare Diseases contained in this report would be an opportunity to further consider this approach.

Any effective policy framework will need to recognise the broader benefits from new therapies, to ensure that we do not compound the challenges associated with an ageing population by denying funding for therapies for rare diseases, and that we are ready to respond to technological developments.

2010 changes to the LSDP

Notwithstanding the relatively small cost of the LSDP, the then Government tightened the criteria for listing new drugs under the scheme in 2010.

This occurred in response to a combination of the high average cost per patient per year of accessing therapies on the LSDP; concerns about the number of new therapies for rare diseases reaching the market, horizontal equity; efficiency and the sustainability of the program.

Since the changes were introduced four years ago, only two new therapies have been approved under the LSDP.

- Vpriv® for Type 1 Gaucher was listed in March 2012 on the basis of cost-minimisation when compared to an existing treatment.

- Soliris® (eculizumab), which was previously approved under the old criteria, was subsequently approved under the new criteria and listed on 1 January 2011.

Aside from these products, no new treatments for rare disease have successfully navigated the entire process for funding rare disease therapies since the reforms in 2010.

The most contentious change in 2010 was the inclusion of Criterion Four, which includes a requirement that there is *acceptable* evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug.

LSDP CRITERIA FOR FUNDING

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 lifesaving 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.

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 a one year period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian.

The subjective nature of Criterion Four has created uncertainty in the industry, with clinicians and for patients. There is inherent ambiguity in the requirement that the therapy offer a substantial extension to life. This is highlighted by the Department of Health's response to a question on notice from Senator Boyce in 2013 asking for the definition of 'substantial':

"Each application is assessed on its merit based on the strength of clinical evidence which is submitted by the pharmaceutical company, tailored to the specific disease."[56]

The ambiguity has created uncertainty, and therefore risk, for companies and patients seeking to gain reimbursement for new therapies and ensure ongoing access to treatment.

The term *acceptable* evidence similarly implies a degree of subjectivity that did not exist previously.

Small patient populations make it difficult to enroll large numbers of patients into standard randomised control trials for rare disease drugs. As a result, clinical trials must be based on smaller groups, unlike as is the case for more common conditions, and it is not at all clear what constitutes *acceptable* evidence in this context. For patients with rare diseases to not be discriminated against, a more flexible approach is needed.

The tightening of criteria for listing new rare disease therapies also raises questions of procedural fairness and the need for transparency in processes, discussed above as part of the ethical considerations of rare disease management.

Implications of the 2010 reforms

Since the 2010 changes, there has been an increasing reliance on listing rare disease therapies under the PBS highly specialised drug program, which does not fully take into account the special nature of therapies for rare diseases. This has led to delays in patients accessing new therapies and created a significant administrative burden.

Patients have had to increasingly rely on compassionate access from pharmaceutical companies to access new therapies. This increases uncertainty and anxiety for already vulnerable patients who cannot rely on ongoing access to new therapies.

Providing compassionate access indefinitely is not sustainable for pharmaceutical companies, which need to recoup the cost of developing new therapies to provide returns to shareholders and fund ongoing investment.

Compassionate access schemes are not conducive to systematic data collection to inform practice.

The reliance on compassionate access by pharmaceutical companies raises serious questions about the expectations of patients suffering from rare diseases given Australia's otherwise universal health system.

We now have the ability to treat many rare illnesses, but are not prioritising funding in this direction. It is within this context that the current review of the LSDP is crucial to Australian suffering from rare conditions.

INTERNATIONAL FINDINGS ON THE DEVELOPMENT OF RARE DISEASE MEDICINES

Only 1 of the 5000 to 10,000 substances initially tested gets through the marketing authorisation phase.

It is estimated that there are between 5000 and 8000 distinct rare diseases.

80 per cent of rare diseases have a genetic cause.

It takes on average 10 to 12 years to develop and bring a new treatment to the market.

SOURCE: *European Biopharmaceutical Enterprises and EuropaBio, Development process of Orphan Medicines, Available at: http://www.europabio.org/sites/default/files/report/development_process_of_orphan_medicines.pd*

8. Aligning Rare Disease Management with the National Medicines Policy

The Australian Government's National Medicine Policy (NMP), which has four central objectives, already provides a framework to underpin the funding of new therapies for rare diseases.

These objectives are: 1) timely access to medicines at an affordable cost to individuals and the community; 2) that medicines should meet quality, safety and efficacy standards; 3) quality use of medicines; and 4) maintaining a responsible and viable medicines industry.

While the policy for funding therapies for rare diseases should meet these objectives, different policy processes are required compared to the funding of other therapies under the PBS.

In this section we develop a set of policy principles that align with the NMP, and address the specific ethical and operational requirements of therapies for rare conditions.

These principles can be used to assess policy options for the funding of therapies for rare diseases and the extent to which they adhere to the objectives of the NMP.

OBJECTIVE ONE:
Timely access to the medicines that Australians need, at a cost individuals and the community can afford.

Cost-effectiveness

This objective of the NMP is generally interpreted as meaning that medicines should be demonstrated to be cost-effective. In keeping with this, the 2009 LSDP review interpreted Objective One of the NMP as requiring evidence of cost-effectiveness in order to justify the funding of medicines for rare diseases.

In order to be considered for funding under the current program however, a drug must have failed to meet required cost-effectiveness threshold for PBS listing.[57] As such, by definition, the current program does not meet the 'implied' cost effectiveness principle underpinning the NMP.

For reasons described in detail in our ethics framework in section 7, cost-effectiveness alone is not a suitable metric with which to make decisions to fund or not to fund new therapies for rare diseases.

Furthermore, the cost-effectiveness criteria used by PBAC are relatively narrow. Benefits are generally limited to direct benefits for the patient and do not explicitly include the impact on carers. Costs can also be narrowly focused on healthcare costs, rather than taking into account broader care and economic costs.

Underlying the concept of cost-effectiveness used in the PBS is a utilitarian approach to funding. The often-unstated objective is to maximise health across the community and to do as much good as possible with scarce health dollars.

On the one hand, cost-effectiveness represents perfect horizontal equity – it treats health gains by all individuals equally. However, it ignores vertical equity concerns about different levels of need and how health gains are distributed.

The current cost-effectiveness framework places too much weight on a HTA method that effectively values extending the life of a 90 year old equally with that of a 1 year old.

These are inherently difficult trade-offs for society, practitioners, and Government. The cost-effectiveness framework used by PBAC necessarily simplifies this trade-off, and as a result the distribution of health across the community can be uneven in terms of access to therapies for patients of rare diseases.

Because of the small numbers of patients living with rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to recognise the needs of Australians with very rare conditions.

Difficulties faced by those with rare diseases include the vulnerability of small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers making a reasonable return on their research and

development investment because of the very small populations treated.

For solid policy reasons, cost-effectiveness alone is therefore not a suitable metric with which to make decisions to fund or not to fund new therapies for rare diseases.

Modifications are required in order to adapt cost-effectiveness analyses to the funding of rare diseases. The standard PBS cost-effectiveness analysis could, for example, be explicitly expanded for therapies for rare diseases to include impact on carers, broader community care and economic costs.

Enriching cost-effectiveness in this way would better inform decision makers on the true costs of listing or not listing new drugs for rare diseases.

Budget sustainability

As with any health technology, the cost of funding therapies for rare diseases needs to be sustainable within the broader health and social welfare budget.

Unlike the criteria for general PBS listing, the current criteria for funding a new therapy under the LSDP does not refer to the budget cost to list a new therapy. However in the current fiscal environment arguably all expenditures are increasingly under the scrutiny of governments.

However, as explained previously, while per unit costs of drugs for rare diseases are generally higher than other medicines funded under the PBS, small patient populations mean that the total budget cost is often relatively low.

The current budget cost of the LSDP is approximately $80 million within the context of a $64.5 billion health budget.

Notwithstanding this small relative cost, the cost of funding therapies for rare diseases needs to be sustainable within the broader health and social welfare budget.

Furthermore, a narrow focus on the budget impact of funding therapies for rare diseases ignores the broader economic and social costs of not providing

access to new therapies for those suffering rare and life threatening conditions. For example, it provides no consideration of the impact on the carers of those with rare conditions (both quality of life and economic loss).

Providing early access to new therapies has the capacity to reduce long-term care needs and costs, reducing budget pressures elsewhere in the system, and these factors should be included in any assessment of new therapies.

Similarly, we have seen in the context of the National Disability Insurance Scheme, an appreciation of the lifelong cost of disability, and the importance of early intervention, and these factors apply equally to drugs for rare diseases.

While such an expansion will not make the funding of many therapies for rare diseases cost-effective at a whole population level, it will better reflect the true cost of providing Australians suffering rare diseases access to life saving and life changing treatments.

OBJECTIVE TWO:
Medicines meeting appropriate standards of quality, safety and efficacy.

Both the Therapeutic Goods Agency (TGA) and PBAC require evidence on quality, safety and efficacy in order for drugs for rare diseases to gain access to the Australian market and be funded.

However, there will always be differences in the quality of this evidence between therapies for rare diseases and therapies for more common conditions.

Assessing effectiveness

A number of issues make it difficult to obtain good quality evidence on the effectiveness of drugs for rare diseases compared with therapies for more common conditions.

First, it is often not possible to recruit an adequate

sample size to test treatments for very rare diseases through gold standard randomised control trials. For example, a trial of itraconazole for the prevention of severe fungal infection in children and adults with chronic granulomatous disease, took 10 years to recruit just 39 patients.[58]

Second, drug trials for rare diseases are often halted early on ethical grounds when interim analysis demonstrates clinical superiority on an outcome measure such as survival. In such cases, continuing with a placebo group would be deemed unethical.

Third, the clinical evidence on drugs for rare diseases is often based on short-term surrogate outcomes rather than long-term effectiveness. Heterogeneity of some of the conditions means finding populations with same clinical base lines is also challenging.

As a result, extrapolation and modeling of clinical outcomes is often used in submissions for listing to estimate the long-term benefits and cost-effectiveness of therapies for rare diseases. This creates uncertainty around actual outcomes.

There is currently no rare disease registry or rare disease policy in place, making it difficult to effectively co-ordinate clinical trial sites in Australia. The development of national or international drug and disease registries that allow long-term follow-up on safety and effectiveness would go part way to addressing these issues.

The utility of these registers is, however, limited by lack of comparator groups, small patient populations within countries, and different approaches and requirements across different jurisdictions. It can also be difficult to identify patients due to misdiagnosis and require long time frames to produce meaningful data sets for analysis.

A more coordinated approach across countries, focused at the disease level would better alleviate Government concerns. International disease registries for rare conditions would provide a broader study population, enhancing

the reliability of findings. They may also provide comparator treatment groups to better evaluate the effectiveness of the particular therapy of interest.

Australia, as a world recognized leader in HTA, is in a good position to lead such efforts through bodies such as the World Health Organisation Department of Essential Medicines and Health Products.

Notwithstanding the development of such registries, is it important to recognise that differences in levels of evidence on clinical effectiveness for therapies for rare diseases, versus more prevalent conditions, are to be expected.

This could be formally acknowledged by the Government being more willing to accept the best available evidence when assessing the effectiveness of new therapies for rare diseases.

OBJECTIVE THREE:
Quality use of medicines.

To ensure value for money, the system developed to fund new therapies for rare diseases should continue to ensure that only those patients that will benefit from treatments have access.

However, Australia continues to lack a holistic rare disease strategy, to tie together the different levels of government and health care provision.

All EU countries under the direction of the European Commission have recently completed orphan drug strategies. These link together the need for early diagnosis, treatment and care options.

A national strategy led by the Commonwealth in consultation with State and Territory Governments, patient groups and industry would improve outcomes for all Australians suffering rare conditions.

Such a strategy would allow consideration of all the issues and costs involved in treating individuals with rare conditions, not just the costs of providing access to rare disease drugs.

OBJECTIVE FOUR:
Maintaining a responsible and viable medicines industry.

Certainty about reimbursement reduces commercial risk and provides a more attractive environment for investment and innovation. It is crucial that the program for funding rare disease therapies into the future and the PBS provide a sufficient degree of certainty to industry through a workable and transparent administration framework.

Ensuring the system for reimbursement of new therapies for rare diseases is accountable, transparent, has integrity, is well coordinated, timely and informed is critical. The framework for funding rare disease therapies must be a fit for purpose assessment approach that takes into consideration all of the issues inherent in rare diseases.

The inherently higher risks associated with research and innovation in the development of therapies for rare diseases (due to lower potential returns from small patient groups and difficulties in establishing effectiveness) make a different approach to rare diseases necessary.

But the administration of the current program for rare disease therapies is falling short of these requirements. A process is needed that is more explicitly responsive to the need to promote ongoing industry investment in new drugs for rare diseases and expands existing HTA processes to reflect a fit for purpose approach to rare disease therapies.

Medical innovation

In proposing the Medical Research Future Fund, the Government has recognised the importance of medical research in containing future health care costs.

Research has indicated that for every dollar invested in Australian health research and development, an average of $2.17 in health benefits is returned.[59]

This applies equally to rare diseases and, furthermore, the benefits of research into rare diseases go far beyond the crucial task of finding treatments for rare diseases.

Rare diseases are now at the forefront of personalised or genomic medicine, which applies genetic information about each patient to tailor treatments to individual needs. Increasingly this allows certain therapies to be targeted specifically to the best responder patient groups, to improve patient outcomes, minimise side effects and reduce costs.

While various Government policies have led to much greater private investment in research and development of drugs for rare diseases, these policies rely on industry being confident that, once developed, these therapies will be funded.

Ensuring certainty of funding for rare disease medications is an important corollary for the successful pursuit of the objectives behind the proposed Medical Research Future Fund, to give certainty to the commercialisation and utilisation of medical innovations.

Administration

For a new therapy to be considered for listing under the current program for rare diseases it must be determined to not meet the PBS cost-effectiveness criteria. This means companies must effectively apply for two separate schemes, even when it is clear that the cost-effectiveness criteria under the PBS will not be met.

Therapies for rare diseases that do meet the cost-effectiveness criteria are generally considered under the PBS's highly specialised drug program. The PBAC is not allowing rare disease therapies through to the current LSDP, but have rather kept them in the PBS system. This approach fails to address the specific issues of rare disease and means the objectives of rare disease policies to ensure access therapies for very small patient groups are less likely to be met.

Even when new therapies are eventually funded, the process can take years and multiple resubmissions to PBAC by industry. These delays result in patients being denied access to new therapies that may save or substantially improve their lives.

Having to submit applications to PBAC for a rejection is unnecessary red-tape and adds to delays in the process for considering the funding of rare disease therapies.

This split and time-consuming process creates uncertainty, time delays and inequities in access. A simpler and fairer system is needed, that would treat all therapies for rare diseases equally through a single process, reducing red tape and improving timeliness.

There are significant differences in the decision-making approaches for funding under the PBS and current rare disease program.

These go beyond specific criteria and the application of cost-effectiveness criteria.

In order to be listed under the current rare disease program a new therapy must meet all eight criteria, and if it fails one then it is denied funding. This is an exceptionally high bar to jump and a major factor in why so few new therapies are being listed under the LSDP.

The process for the PBS is more weighted and nuanced, taking into account how a therapy performs against all criteria. This allows for a new therapy to fail to fully meet one criterion, but still be listed if it performs strongly against other criteria.

Adopting a weighted approach based on broad community and patient values would allow a fairer appraisal of individual new therapies including their strengths and weaknesses. This would provide greater procedural fairness certainty to manufacturers and encourage the development of more therapies into the future to treat rare and life threatening conditions.

9. Improving the Management of Rare Disease Therapies through Multi-Criteria Decision Analysis (MCDA)

Addressing the issues with Australia's current approach to funding therapies for rare diseases and meeting the objectives of the National Medicines Policy requires a multi-faceted approach.

Addressing the issues with Australia's current approach to funding therapies for rare diseases and meeting the objectives of the National Medicines Policy requires a multi-faceted approach.

Australia's use of Health Technology Assessments (HTA) within the PBS has been world leading but its approach to funding therapies for rare diseases is lagging behind international best practice.

The funding of therapies for rare diseases is fundamentally about resource allocation: is the Government's willingness to pay for economic efficiency and horizontal equity– treating those patients that maximise health gain subject to a limited budget – greater than the Government's willingness to pay for allocative efficiency and vertical equity – fairness in society?

Answering this question is complex and standard approaches used by the PBS for HTA need to be tailored to take into account the unique nature of therapies for rare diseases.

Simply increasing the cost-effectiveness threshold for rare diseases is unlikely to be sufficient due to the high price point for new therapies required to make their development commercially viable. A more flexible, fit for purpose process that takes into account a different set of benefits or value than simply a cost-effectiveness threshold is needed.

Such a system would ideally allow the evaluation of treatments for rare diseases on a multi-criteria basis, while allowing the possibility to distinguish between different therapies.

In this section we outline the case for adopting Multi-Criteria Decision Analysis (MCDA) in the assessment of new therapies for rare conditions. We argue that such system would reflect international best practice and better align Australia's system with the principles underpinning the National Medicines Policy.

Multi-criteria decision analysis

The need to balance economic and ethical considerations in the funding of rare therapies involves difficult trade-offs. Decision-making approaches that don't allow for the explicit weighting of these trade-offs give insufficient weigh to competing priorities.

As argued in this report, Australia's current approach, where all eight criteria for the funding of new therapies under the LSDP must be met and a number of important considerations are not included, fails to reflect the complexity of decision-making and international best practice.

One approach that would reflect the complexity of decision-making is Multi-Criteria Decision Analysis (MCDA).

MCDA has been developed for a number of complex decision-making situations and applied to funding of new therapies for rare diseases internationally. As outlined in the analysis of the international context in Chapter 6 of this report, MCDA has recently been adopted by NICE in UK in its decisions around funding ultra-orphan drugs and represents international best practice. It employs the underlying philosophy of HTA assessment while reflecting the unique nature of therapies for rare diseases.

MCDA is a way of looking at complex decisions that are characterised by a mixture of monetary and non-monetary objectives, and of breaking decisions down into more manageable pieces. It would for example allow judgments to be made on individual criteria relevant to rare diseases such as rarity, disease severity or degree of uncertainty around efficacy.

Under MCDA these individual judgments could then be jointly assessed to provide an overall picture for decision makers.

MCDA is both an approach and a set of techniques that orders options from most preferred to least preferred. In the case of funding new therapies for rare diseases in Australia there would effectively be two primary options: to fund or not to fund a new therapy, with potential additional options around conditions attached to the funding of a new therapy.

MCDA allows options to differ in the extent to which they achieve several objectives, and no single options needs to achieve all objectives. This more nuanced approach better reflects the unique nature of therapies for rare conditions and is more closely aligned with the approach adopted in the broader PBS.

ESTABLISHING MCDA:

DETAILED STEPS FOR A SYSTEM TO FUND RARE DISEASES IN AUSTRALIA[60]

1. **Establish the decision context.**

   1.1 Establish aims of the program to fund rare diseases in Australia consistent with the National Medicines Policy, and identify decision makers and other key players.

   1.2 Design the system for conducting the MCDA, using NICE's new system in the UK to fund ultra-rare orphans and the PBAC process for the PBS as a basis.

2. **Identify the process for selecting new therapies to be appraised.**

3. **Identify objectives and criteria.**

   3.1 Identify criteria for assessing the funding of new therapies for rare diseases in Australia through consultation with patients, the public and industry.

   3.2 Organise the criteria by clustering them under high-level and lower-level objectives in a hierarchy.

4. **'Scoring': Assess the expected** performance of each therapy against the criteria then assess the value associated with the consequences of each option for each criterion.

   4.1 Describe the consequences of funding each therapy.

   4.2 Score the therapies against the criteria.

   4.3 Check the consistency of the scores on each criterion.

5. **'Weighting': Assign weights for each of the criterion to reflect their relative importance to the decision.**

6. **Combine the weights and scores for each option to derive an overall value.**

   6.1 Calculate overall weighted scores at each level in the hierarchy.

   6.2 Calculate overall weighted scores.

7. **Examine the results.**

8. **Sensitivity analysis.**

   8.1 Conduct a sensitivity analysis: do other preferences or weights affect the appraisal of therapies?

   8.2 Look at the advantage and disadvantages of funding or not funding therapies.

Importantly MCDA explicitly and transparently provides for trade-offs between objectives, such as efficiency and equity, or long versus short-term costs. This is well suited to consideration of funding of rare diseases where many such trade-offs are required. For example, where costs today in funding new treatments for rare diseases may be partly offset by reduced spending on health and community care services in the future.

In MCDA, an expert panel generally defines the relevant decision-making criteria and their relative importance. In the case of the system in Australia, this could be done in consultation with industry, patients and the community.

Each criterion needs to be measurable, so that the degree to which a therapy for a rare condition attains the objective can be assessed. The scores on the different criteria can then be aggregated with a view to calculating the overall performance of the therapy.

Importantly for rare diseases, MCDA systematically considers additional criteria beyond cost effectiveness, such as societal preferences, equity and benefits to care givers, disease rarity and severity, rule of rescue, availability of alternative health technologies, impact of drug on disease, clinical evidence, and manufacturing complexity.

While some of these criteria are included in the current program for rare diseases, MCDA would provide a more complete and robust framework for consideration.

Crucially, it would mean that no single criterion determined the outcome of an assessment. Whereas currently all eight criteria must be met in order for a new therapy to be funded, a MCDA approach would be more balanced.

While detailed work and consultation would be required to implementing such an approach in Australia, the current experience of NICE in England could be used as a starting point. Steps that would be required for such a system in Australia are outlined above, and provide an overview of a potential process including the need

for consultation to reflect community and patient values.

While MCDA may be viewed as a time consuming approach given the limited budget impact of a many new therapies for rare disease in Australia, it does comprehensively address the complexity of funding therapies for rare diseases, and would help sustainably manage the funding of drugs for rare diseases into the future.

Meeting policy objectives

A system using MCDA would better meet the National Medicines Policy objectives and align more closely with the economic and ethical considerations identified in this report than the current system. MCDA provides an opportunity for a much broader understanding of cost effectiveness and a more balanced decision making approach reflecting community values, patient needs and delivering greater equity in access to treatments.

An MCDA approach may still result in delays in access for patients with rare conditions. This consideration needs to be weighed against the need to ensure ongoing sustainability of the system and confidence in the integrity of the process for funding rare disease therapies.

Under an MCDA approach, short-term costs may be higher due to more new therapies being funded. However in the long-term, health and social care costs may be reduced through access to new drugs and treatment of rare diseases. An MCDA approach would also improve the viability of the medicines industry in Australia through providing greater transparency and certainty as to which new therapies are likely to be funded and under what conditions.

	Timely access to the medicines that Australians need, at a cost individuals and the community can afford				Medicines meeting appropriate standards of quality, safety and efficacy	Quality Use of Medicines	Maintaining a responsible and viable medicines industry
	Timely Access	**Cost-Effectiveness**	**Rule of Rescue**	**Budget Sustainability**			
Current LSDP	**LOW** Significant delays in accessing treatment	**LOW** Cost Effectiveness does not form part of current assessment under LSDP	**LOW** Current processes limits access through requiring that all 8 criteria are met, and places unrealistic hurdles for listing under Criteria Four	**MEDIUM** No consideration of broader social and economic costs increases long term costs for treating and caring for those with rare conditions	**HIGH** All therapies must be safe and effective by the TGA to be funded	**MEDIUM** While access to the therapies funded under the scheme is linked to clinically assessed need, the lack of broader strategy for rare diseases potentially reduces effectiveness	**LOW** Lack of certainty and transparency placing viability of ongoing development of new therapies and marketing of these therapies in Australia under risk
Multi-Criteria Decision Analysis	**LOW** While this approach may be more likely to provide access to new therapies, it is likely to continue to involve delays	**HIGH** Would expand current criteria to include consideration of a broader concept of cost effectiveness	**HIGH** A weighted approach to decision making would reflect the unique nature of rare disease drugs	**MEDIUM** While costs for funding therapies for rare diseases may be higher, there would be broader consideration of the economic and social costs of funding new drugs	**HIGH** All therapies must be safe and effective by the TGA to be funded	**MEDIUM** While access to the therapies funded would be linked to clinically assessed need, the absence of a broader strategy for rare diseases potentially reduces effectiveness	**HIGH** A weighted approach including broader assessment of the economic and social costs and benefits would provide greater certainty to industry that new therapies would be funded

Funding the additional expenditure

One of the issues for Government funding of new therapies for rare diseases is managing the uncertain costs of new therapies.

It is not possible to know what new therapies are going to become available in the future and place additional spending pressure on the budget.

The Government's proposed Medical Research Future Fund demonstrates the Government's intention to support medical research and innovation. To maximise the benefit of this investment it is also necessary to have a system in place that will bring products developed through the Medical Research Fund to market.

Development of medications won't suffice; consideration needs to be given to the commercialization of medical innovations.

As noted above, the very small proportion of current Commonwealth health expenditure currently allocated to rare disease therapies (just 0.2 per cent) mean that even with a more effective system for funding rare disease therapies, the very small patient populations mean that the level of expenditure growth will remain low.

Further, the small levels of expenditure required to effectively fund rare disease medications are necessary to not only ensure Australia's health system continues to meet the needs of all Australians, but the principles of horizontal and vertical equity are achieved.

Ensuring funding for rare disease medication into the future is critical to both the wellbeing of Australians suffering from rare diseases and their families, and the future of rare disease innovation in Australia.

10. Conclusion

In many ways the future for those suffering rare diseases in Australia has never been brighter, with the prospect of more innovative therapies being discovered than ever before.

These new therapies offer the prospect of saving, extending and drastically improving the lives of thousands of Australians that suffer from rare diseases.

However, under Australia's current system many Australians will never be able to afford to access these treatments.

Australia's system for funding rare disease drugs requires reform to better meet the needs of patients, Government and industry.

This report provided an overview of the policy context within which the current program for funding rare disease therapies, the LSDP, operates, and highlighted the special case of therapies for rare conditions.

An exploration of the policy context highlighted the need for a more holistic approach to rare diseases in Australia that should be informed by a national strategy on rare diseases. This strategy would cover research, diagnosis, new therapies, treatment and ongoing care for those suffering from rare conditions.

RECOMMENDATION I:

The Australian Government should develop a National Strategy for Rare Diseases that provides a holistic approach to rare disease management.

The research undertaken for this report found that Australians with rare diseases are not only being denied access to new therapies funded overseas, they are also waiting significantly longer for access to new therapies. On average Australians are waiting between 2 – 4 years longer for access to government funded treatments for rare diseases than in comparable countries. Some medications remain unavailable 8 years after becoming available overseas.

A review of the systems of rare disease management in a number of comparable countries was also undertaken and revealed a range of developments in processes, definitions, evaluation frameworks being adopted. Australia must reflect global developments in rare disease management in the development of its strategy to ensure Australia remains a world leader in health policy and services.

RECOMMENDATION 2:

Australia should be mindful of international practice and developments when setting rare disease policy frameworks.

The unique circumstances of rare diseases and patient groups necessitate reform of the system for approving rare disease therapies. The current system for funding therapies for rare conditions is failing to meet the four objectives of the National Medicines Policy: timely access to medicines at an affordable cost to individuals and the community; that medicines should meet quality, safety and efficacy standards; quality use of medicines; and maintaining a responsible and viable medicines industry.

A system that incorporates MCDA may better align Australia's system with the objectives of the National Medicines Policy, the identified guiding principles and international best practice.

RECOMMENDATION 3:

A more flexible analysis of cost-effectiveness should be adopted in the assessment of new therapies that balances other considerations such as equity, the rule of rescue, community values, patient needs and the long-term avoided costs of access to treatment. Consideration should be given to using Multi-Criterion Decision Analysis as a decision-making framework with decision weights based on community and patient values.

Australia is a world leader in terms of health services and medical innovation and the policy framework that supports this system must continue to meet patient, community and industry expectations for transparent, trusted and equitable processes. Such processes are not only necessarily to reflect the complexity of rare disease therapies but also give confidence and certainty to patients and the health sector.

Australia has a significant medical research capacity and the Government's support for medical research and innovation necessitates a process for rare disease management and funding into the future.

RECOMMENDATION 4:

The unique nature of therapies for rare diseases, including small patient populations and the implications this has for clinical trials, should be recognised in the evidence requirements for funding. This is necessary to address uncertainty in current processes for the development and funding of rare disease therapies in Australia.

Absent a fit for purpose process for rare disease management, involving patients, clinicians, community and the sector, Australia risks missing an opportunity to not only manage the cost of treatment, including through reduced hospitalisations and improved patient outcomes, but will also risk Australia's reputation as a world leading health system

RECOMMENDATION 5:

The process for assessing new therapies for rare diseases should be efficient, fit-for-purpose, transparent and informed by community and patient values. This is necessary to ensure the trustworthiness and legitimacy of decisions about funding new therapies for rare diseases, that

This report seeks to strike a balance in the economic and social values that must necessarily be factored into the management of rare diseases. The proposed ethical framework contained in this report seeks to address the issues of both horizontal and vertical equity, critical to sustainable access to treatment for rare disease patients. This approach also provides guidance for Government policy on the funding of rare disease therapies in a manner consistent with the National Medicines Policy objectives.

If adopted, the recommendations contained in this report will ensure rare disease patients have greater confidence and certainty in being able to access the standard of care and health services that the majority of Australians often take for granted. This is a foundation of the Australian health care system and one the community supports being available to all Australians, including those living with rare diseases.

Glossary

ALLOCATIVE EFFICIENCY: When resources and production are arranged so the benefit is maximised from the available resources – in other words the health sector provides society with the amounts and types of health care that they most prefer.[61]

COST-EFFECTIVENESS: A type of economic evaluation that compares options that have a common health outcome. The output is generally displayed as cost per unit of effect. Unlike a cost-benefit analysis it does not require that health consequences be translated into dollar amounts.[62]

DISTRIBUTIVE JUSTICE: The distribution of societal goods, including healthcare benefits, in an ethically sound manner.

EFFICACY: The performance of a health care option under highly controlled circumstances.[63]

EFFICIENCY: Making the best use of available resources.[64]

EFFECTIVENESS: This refers to the performance of a health care option in the real world with a wide variety of providers.

EQUITY: Fairness in the allocation of resources between individuals or groups.[65]

HORIZONTAL EQUITY: The equal treatment of equals, demonstrated when services are equally accessible to everyone in the community with a similar level of need.[66]

OPPORTUNITY COST: The opportunity cost is what must be given up in order to obtain something (i.e. the value of time or any other input in its highest value use).[67]

RARE DISEASE: A life threatening or chronically debilitating condition that only affects a very small number of people in the population.

RULE OF RESCUE: The moral and psychological imperative to help those in dire need. More formally, the PBAC guidelines set out the criteria for a claim of rule of rescue that includes that no alternative exists in Australia to treat patients with the specific circumstances.[68]

UTILITARIANISM: The doctrine that an action is right in so far as it promotes happiness, and that the greatest happiness of the greatest number should be the guiding principle of conduct.[69]

VERTICAL EQUITY: The unequal but equitable ('fair') treatment of unequals, demonstrated when services account for the special needs of particular groups in the community and adjust aspects of service delivery to suit these needs. This approach may be needed where geographic, cultural or other reasons mean some members of the community have difficulty accessing a standard service.[70]

The Authors

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Amanda has played a central role in the Federal Government's Budget Strategy, was responsible for delivery of key budget policies, and advised on expenditure programs across a range of areas including health reform. Additionally Amanda was a senior adviser in the PNG Department of Treasury from 2006 to 2008 and has extensive experience working with and advising the not for profit sector domestically and internationally.

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Dr Wendy Lipworth is a bioethicist and health social scientist. She completed her medical degree at UNSW in 1999, and moved into academia in 2002. She has since completed a MSc by research (USYD) on biobanking ethics; a PhD (USYD) on the ethics of journal peer review; and a Postdoctoral Fellowship at UNSW on pharmaceutical policy. She is a Senior Research Fellow & NHMRC Career Development Fellow at the Centre for Values, Ethics and the Law in Medicine.

Dr Lipworth has published over 50 peer reviewed journal articles in ethics, social science, legal and medical journals, and her research has been presented both nationally and internationally.

Her work has also been translated into policy and practice through her role as Deputy Chair of the Australian Bone Marrow Donor Registry (ABMDR) Ethics Committee, and her involvement in the NSW Ministry of Health's Office for Health and Medical Research (OHMR) Working Group on consent for NSW public health biobanks; the latest revision of the Royal Australasian College of Physicians' conflict of interest guidelines; and two submissions by professional organisations to the Pharmaceutical Benefits Advisory Committee. In 2013 she became the inaugural Chair of a Special Interest Group on ethics for the Drug Information Association – a major, global, non-profit organisation with more than 18,000 members worldwide who are involved in the development and regulation of pharmaceuticals.

She is an Associate Editor for the *Journal of Bioethical Inquiry and Therapeutic Innovation and Regulatory Science*.

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Angela is an experienced public sector economist who has worked at the highest levels of Government. Currently completing a PhD in health economics at Monash University, Angela has specialised knowledge of the health sector alongside an intimate understanding of Government.

Angela worked in the Department of the Prime Minister and Cabinet as an Economic Policy adviser. In this role Angela directed and undertook economic analysis related to workplace relations, taxation and superannuation and on the Work and Family Taskforce.

Angela was also Senior Advisor and Deputy Chief of Staff to the Australian Minister for Finance and Deregulation from November 2007 to September 2010. In this role Angela advised the Minister on fiscal policy settings and social policy and participated in Cabinet level meetings. Angela was also the lead adviser to the Minister on 2010 Health Reforms that redefined responsibilities between State and Federal Governments and ensure sustainable funding of healthcare.

Angela has presented research at major conferences including 'Choice and Competition in Social and Health Care Markets: Impact on Quality, Cost and Access' and at the National Disability Services Research to Action Conference in May 2014. In addition to studying for her PhD, Angela has a Master's of Science (Health Economics) from the London School of Economics and Political Science, a Bachelor of Commerce with Honours in Economics from the University of Melbourne and a Bachelor of Economics, University of Tasmania, Major in Analytical Economics, 2000.

Footnotes

1. Two therapies have been funded under the LSDP since 2010. Vpriv for Type 1 Gaucher was listed in March 2012 on the basis of cost minimisation when compared to an existing treatment. Soliris was funded in January 2011. It was first approved under the pre-2010 funding criteria at March 2009 PBAC meeting. In May 2010, the Department of Health referred Soliris back to PBAC for review under the new LSDP entry criteria.

2. For example, Myozyme, a late onset Pompe disease therapy, was listed in England, Netherlands and Germany in 2006 and is still awaiting approval in Australia 8 years later. See Table 2 below for further listing information.

3. The equivalent of 1 in 10,000 persons is commonly referred to in terms of Australia's rare disease definition. Updating for current population this would be closer to 1 in 11,500 persons.

4. The equivalent of 1 in 10,000 persons is commonly referred to in terms of Australia's rare disease definition. Updating for current population this would be closer to 1 in 11,500 persons.

5. Rare Voices Australia Ltd's Fact Sheet available at: http://rva. blob.core.windows.net/assets/uploads/files/A4_RVA_Fact_ Sheet.pdf

6. 6. Aymé, S. and C. Rodwell, *Report on the state of the art of rare disease activities in Europe of the European Union Committee of Experts on Rare Diseases - Part I: Overview of rare disease activities in Europe and key developments in 2010*. http://www.eucerd.eu/upload/file/Reports/2011ReportStateo fArtRDActivities.pdf. Reported in the Western Austalian Rare Disease Strategy 2014-2018.

7. For further information on the LSDP see the Department of Health's website available at: http://www.health.gov.au/lsdp

8. For further information see the Department of Health website at: http://www.pbs.gov.au/info/browse/section-100/s100-highly-specialised-drugs

9. See http://www.health.gov.au/internet/ministers/publishing.nsf/ Content/health-mediarel-yr2014-dutton030.htm

10. For further information on the National Medicines Policy see the Department of Health's website available at: http://www.health. gov.au/nationalmedicinespolicy

11. Australian Government 2014-15 Budget Paper No.1 Statement 6: Expenses and Capital Expenditure, May 2014

12. This figure excludes funding for the Herceptin program which was established as a special fund beyond the LSDP. Advice to industry indicates that the annual cost of the core LSDP is around $80 million per annum.

13. Australian Government 2014-15 *Budget Paper No.1 Statement 6: Expenses and Capital Expenditure*, May 2014

14. Australian Government 2014-15 *Budget Paper No.1 Statement 6: Expenses and Capital Expenditure*, May 2014

15. http://www.cadth.ca/products/environmental-scanning/ environmental-scans/environmental-scan-42

16. See http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/_2012/2012-147a-eng.php

17. See http://ec.europa.eu/health/rare_diseases/policy/index_ en.htm

18. See: http://rarediseases.info.nih.gov/gard/browse-by-first-letter/

19. Lipworth W, Ho K, Kerridge I, Day R: Drug policy at the margins: The case of growth hormone replacement for adults with severe growth hormone deficiency. Med J Aust 2012, 197(4):204-205.

20. Largent EA, Pearson SD: *Which ORPHANS Will Find a HOME? The Rule of Rescue in Resource Allocation for Rare Diseases*. Hastings Cent Rep 2012, 42(1):27-34

21. Forsythe LP, Szydlowski V, Murad MH, Ip S, Wang Z, Elraiyah TA, Fleurence R, Hickam DH: A systematic review of approaches for engaging patients for research on rare diseases. *J Gen Intern Med* 2014, 29 Suppl 3:S788-800.

22. McCabe C, Claxton K, Tsuchiya A: Orphan drugs and the NHS: should we value rarity? *Br Med J* 2005, 331(7523):1016-1019.

23. Kesselheim AS, Myers JA, Avorn J: Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer. *Journal of the American Medical Association* 2011, 305(22):2320-2326.

24. Nord E, Richardson J, Street A, Kuhse H, Singer P: Maximizing Health Benefits Vs Egalitarianism - An Australian Survey of Health Issues. Soc Sci Med 1995, 41(10):1429- 1437; Richardson J, Sinha K, Iezzi A, Maxwell A: Maximising health versus sharing: Measuring preferences for the allocation of the health budget. *Soc Sci Med* 2012, 75(8):1351-1361; Richardson J. Critique and some recent contributions to the theory of cost utility analysis. *Working Paper 77*, Melbourne: Centre for Health Program Evaluation, 2007; Gallego G, Taylor SJ, McNeill P, Brien J-AE: Public views on priority setting for High Cost Medications in public hospitals in Australia. Health Expect 2007, 10(3):224-235.

25. Daniels N: Accountability for reasonableness - Establishing a fair process for priority setting is easier than agreeing on principles. *Br Med J* 2000, 321(7272):1300-1301.

26. Wiseman V, Mooney G, Berry G, Tang KC: Involving the general public in priority setting: experiences from Australia. *Soc Sci Med* 2003, 56(5):1001-1012.

27. Or approximately 1 in 11, based on current population figures for Australia. See http://who.int/gho/publications/world_health_ statistics/2014/en/ pp 166

28. The Therapeutic Goods Administration defines a rare disease as effecting less than 2000 Australians, which converts to a population incidence of approximately 1 in 10,000.

29. Defined as affecting less than 200,000 Americans which translates to approximately 1 in 1500 See: http://rarediseases. info.nih.gov/gard/browse-by-first-letter/

30. In Canada rare disease is defined as 5 in 10,000 or the equivalent of 1 in 2,000. See http://www.hc-sc.gc.ca/ahc-asc/ media/nr-cp/_2012/2012-147a-eng.php

31. In the EU rare diseases are defined as 1 in 2,000 persons, See http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

32. South Korea defines a rare disease as affecting less than 20,000 people, or 1 in 2,500 persons. See http://www.cadth. ca/products/environmental-scanning/environmental-scans/ environmental-scan-42

33. Mestre-Ferrandiz, J., Sussex, J., Towse, A.: *The R&D Cost of a*

New Medicine. Office of Health Economics, London (2012)

34. Rare Diseases Impact Report: Insights from patients and the medical community, Shire (2013)

35. For example, recent listings on the PBS for new treatments for cystic fibrosis and aHUS are estimated to have costs per year of this order. See: https://www.health.gov.au/internet/ministers/publishing.nsf/Content/913055A3F0B2D9E0CA257D7E00006B89/$File/PD092.pdf

36. For further information on the 2009 review see http://www.health.gov.au/internet/main/publishing.nsf/Content/lsdp-preview

37. The proposal for a whole of government strategy or national plan for rare diseases has been advocated by many groups, organisations and the health industry for many years. For instance see http://www.apsu.org.au/assets/workshops/rare-diseases/JPCH-Call-for-a-national-plan.pdf and https://www.rarevoices.org.au/news/26/rare-diseases-need-a-national-plan

38. Federal Ministry for Health. National Plan of Action for People with Rare Diseases Action Fields, Recommendations and Proposed Actions 2013

39. Where prices are set in reference to existing therapies.

40. Currently 87 orphan therapies are designated by the EC.

41. Ministry of Health, Welfare and Sport. *Strategy of the Netherlands in the Field of Rare Diseases*. The Hague. 2013

42. National Institute for Clinical Excellence. *NICE Citizens Council Report Ultra Orphan Drugs*. London, NICE, 2004.

43. Youngkong S,Baltuseen R, et al. MCDA for Including Health Interventions in the Universal Health Coverage Benefit Package in Thailand Value in *Health* 15 (2012) 961-970

44. See full process and methods document at http://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/Highly-Specialised-Technologies-Interim-methods-and-process-statements.pdf

45. UK Bio-Industry Association, *Very Rare Diseases, complex issues: Future evaluation of ultra-orphan medicines in the UK*, March 2014 Available at: http://blog.bioindustry.org/2014/03/11/very-rare-diseases-complex-issues-evaluating-orphan-and-ultra-orphan-drugs/

46. Canadian Agency for Drugs and Technologies in Health. *Common Drug Review Update* – Issue 103. May 2014

47. See full process and background document at: www.health.gov.on.ca/en/pro.programs/drugs/how_drugs_approv/review_rare_diseases.aspx

48. Mi, Su. Pharmaceutical Reimbursement Process in Korea: Current and Future. Global Forum.

49. The budget figures presented in Figure 1 also include the cost of the Herceptin program which was a special fund outside of the LSDP. Consequently the $138 million reported in the Budget for LSDP less the Herceptin special fund is $80 million per annum. The chart reflects the cost of Herceptin and LSDP to ensure consistency with budget papers.

50. Australian Government 2014-15 *Budget Paper No.1 Statement 6: Expenses and Capital Expenditure*, May 2014

51. Drummond M, Wilson D, Kanavos P, Ubel P and Rovira J. Assessing the economic challenges posed by orphan drugs *International Journal of Technology Assessment in Health Care*, 23:1 (2007), 36-42

52. National Commission of Audit Report, Available at: http://www.ncoa.gov.au/report/appendix-vol-1/9-3-pathway-to-reforming-health-care.html

53. Note this includes cost of Herceptin program. *Australian Government 2014-15 Budget Paper No.1 Statement 6: Expenses and Capital Expenditure*, May 2014

54. *Australian Government 2014-15 Budget*, Available at: http://www.budget.gov.au/2014-15/content/overview/html/overview_12.htm

55. Merlin T, Farah C, Schubert C, Mitchell A, Hiller J and Ryan P. Assessing Personalized Medicines in Australia: A National Framework for Reviewing Codependent Technologies *Med Decis Making* 2013 33: 333

56. Answer to Senate Estimates Question on Notice, Health and Ageing Portfolio, Budget Estimates 2013-14, Available at: http://www.aph.gov.au/~/media/Estimates/Live/clac_ctte/estimates/bud_1314/DoHA/Answers/129.ashx

57. Thresholds can vary for therapies for rare and life threatening conditions.

58. Lagakos SW. Clinical trials and rare diseases. *N Engl J Med* 2003; 348:2455

59. Exceptional Returns: The Value of Investing in Health R&D in Australia II, 2009.

60. Adapted from Table 6.1, page 50 in *Multicriteria Analysis: A Manual Communities and Local Government*, January 2009

61. National Health and Medical Research Council (NHMRC), Endorsed July 2001, How to compare the costs and benefits: evaluation of the economic evidence, Handbook series on preparing clinical practice guidelines. Available at: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp73.pdf

62. Ibid. NHMRC

63. Ibid. NHMRC

64. Ibid. NHMRC

65. Ibid. NHMRC

66. National Health Pricing Authority (NHPA), *National Health Reform Performance and Accountability Framework*, Available at: http://www.nhpa.gov.au/internet/nhpa/publishing.nsf/Content/1CF48F88798490D8CA257B1A0013576F/$File/121105-PAF-for-web.pdf

67. Ibid. NHMRC

68. Australian Government Department of Health, *PBAC Guidelines*, Available at: http://www.pbac.pbs.gov.au/section-f/f3-other-relevant-factors.html

69. Oxford Dictionary, http://www.oxforddictionaries.com/definition/english/utilitarianism

70. Ibid NHPA