June 2023

Medicines Australia's Submission to the Health Technology Assessment Policy and Methods Review – Consultation 1

A Healthcare System for the 21st Century

Medicines Australia

Executive Summary

A once-in-a-generation opportunity for bold reform

The Health Technology Assessment (HTA) Policy and Methods Review is a key priority of Medicines Australia's *Strategic Agreement with the Commonwealth*, and we welcome the opportunity to contribute to this important consultation. Australia's HTA system was first established in 1993, and it was world-leading at the time. So much has changed over the past three decades that it is now time for a re-evaluation of how we assess medicines for reimbursement.

Patient and public expectations of our health system have risen. Medicines technology has moved beyond traditional chemical compounds to include monoclonal antibodies, companion diagnostics and devices, cell and gene therapies, as well as advanced vaccines technologies, artificial intelligence and digital health solutions. The *Inquiry into approval processes for new drugs and novel medical technologies in Australia* elicited a huge response from patient groups in particular, clearly and urgently articulating the challenges they face in obtaining timely access to medicines.

The HTA Review now gives us the opportunity to fulfil the vision set out in the *National Medicines Policy* (NMP*)*, to achieve the world's best health, social and economic outcomes for all Australians. The COVID-19 pandemic has shown us that investment in medicines and vaccines is an investment not only in health but in the economy; however, as outlined in *The New Frontier Report*[1], the *Inquiry into approval processes for new drugs and medical technologies in Australia* found that we can do better in providing timely and equitable access. This means there should be no delay in subsidised access for patients once a product has been registered as safe and effective.

Medicines Australia acknowledges that the HTA Review is one in a series of recent policy initiatives aimed at improving Australia's health system. The review of the *National Medicines Policy*, *The New Frontier Report*, and the *Strategic Agreement* are all referenced throughout this submission as they entail workstreams which are inextricably linked to the current HTA Review and support many of the recommendations in this submission.

Australia can afford the world's best health

Australia is on the cusp of adopting a new range of remarkable medical innovations with the potential for curative and preventative effects. The Pharmaceutical Benefits Scheme (PBS) needs to be able to accommodate these new technologies for the benefit of Australians. The Australian Government, working constructively with industry over the past two decades, has reformed the PBS to deliver

1 https://www.aph.gov.au/Parliamentary_Business/Committees/House/Health_Aged_Care_and_Sport/Newdrugs/Report

considerable savings; however, there has been no real growth in pharmaceutical expenditure over the past decade or more[2]. Today Australia has an opportunity to use the savings generated to invest in the PBS and lock-in the benefits of these reforms to ensure that Australians do not have to wait any more for new medicines and vaccines. Ensuring that Australians are among the first in the world to access new technologies will require a policy framework that includes enablers for immediate subsided access through HTA policy reforms via the HTA Review.

There are numerous options for reform, both bold and pragmatic

Medicines Australia's submission is structured according to the seven consultation questions. In each chapter we respond to the question and present a range of solutions to the issues raised. In Chapter 1 we highlight the features of the system that are currently working well and should be retained. In Chapter 2 we describe the barriers to earliest possible access, covering HTA policies, HTA methods and some related issues. In Chapter 3 we describe barriers to equitable access, with a focus on cell and gene therapies, rare disease therapies and genomics. In Chapter 4 we discuss elements that detract from person-centredness. Chapter 5 describes perverse incentives. Chapter 6 covers the international perspective and elements of different systems that could work well in Australia (with more detailed information presented in an Appendix). Finally, in Chapter 7 we present a range of reform ideas for consideration that could work together or separately to speed up access, achieve first time success through the PBAC process, and ensure that Australia is a first launch country.

Overarching Recommendations

Key Recommendation 1

The HTA Review should ensure that we meet the vision of the NMP, as informed by *The New Frontier Report*. This will require a commitment to the principle that investing in medicines secures valuable health, social and economic benefits for all Australians, and that this should be reflected in HTA policy and methods.

Key Recommendation 2

Bold and pragmatic reform should be undertaken to remove the patient access gap so that patients can access medicines as soon as possible after TGA registration. This can be achieved by embracing the concepts outlined in the HTA Review terms of reference – faster, more equitable access, patient-centricity and alignment with international best practice.

There are numerous options for reform, which would address issues in three key areas:

A. Commit to delivering faster access for patients through policy and process reform, by:
    - Ensuring all assessment and recommendation processes are aligned to allow for reimbursement from TGA registration.

[2] Biointelect, Shawview Consulting. Funding Innovative Medicines. Australia; 2023

- Introducing interim funding for certain medicines.

B. Reform the HTA system to better enable first time success through the PBAC process, by:
   - Frontloading the system through earlier engagement, including patient involvement.
   - Streamlining the interactions of the HTA Committees.
   - Introducing an independent price negotiation process to expedite access for certain medicines, to be mutually agreed.
   - Expanding the current independent review mechanism, or considering an independent appeals process.
   - Ensuring there are agreed, transparent metrics for HTA processes to enable faster access.

C. In addition to the above recommendations, ensure Australia is a first launch country, by:
   - Establishing innovation incentives.
   - Exploring co-developed international work sharing.

Medicines Australia looks forward to working with the Government, patients, carers and clinicians on this historic opportunity. Together we can achieve our shared goals of:

- reducing the time to access for Australian patients
- improving the attractiveness of Australia as a first-launch country
- ensuring that our assessment processes keep pace with rapid advances in health technology.

Should the Reference Committee have any questions about this submission, please do not hesitate to get in touch. Inquiries can be directed to Anne-Maree Englund (Head of Strategic Policy Implementation) at anne-maree.englund@medicinesaustralia.com.au.

Elizabeth de Somer
CEO Medicines Australia

Summary of Recommendations under each Question

Q1 – Elements that are working effectively

1. The parallel process works well but could be even more effective in reducing time to access by, for example, the **removal of the requirement for a TGA Delegate Overview at time of PBAC decision.**
2. Special pricing arrangements and confidential pricing for medicines are important and **should be retained**.
3. **Transparency operates well in parts of the system but should be improved** to enhance predictability.

Q2 – Barriers to earliest possible access

HTA Policies

Willingness to Invest in Medicines

4. While the PBAC should retain flexibility in the application of ICER thresholds, **willingness to invest in medicines warrants higher ICER ranges**, which the PBAC should be willing to recommend. The ICER ranges should then be tracked and published by the Government across broad disease areas and clinical settings.

Defining Time to Access

5. There should be **agreement from all parties** that time to patient access for medicines means the time from when an innovative medical technology (including medicines, biotherapeutics and vaccines) is registered with the TGA to when it becomes available to patients on the PBS.
6. The Department of Health and Aged Care should introduce integrated and agreed data metrics and a **comprehensive system for measuring the time to patient access**, and report publicly in line with the National Medicines Policy.

Broadening the Valuation of Medicines

7. **Broaden the HTA valuation** from a direct health sector patient perspective to include a health and welfare patient and carer perspective, including those with a direct (and indirect) impact on the Australian Government budget.
8. Develop agreed criteria for situations where **second-order effects** on patients and their caregivers, such as social welfare and carer impacts, should be included in the HTA assessment process, including workable methodologies for the **transparent inclusion of second-order effects** or patient benefits , in a way that supports equity of access.

Lowering the Discount Rate

9. **Lower Australia's discount rate in line with international best practice** to recognise the value of preventative treatments and cures and speed up access to them.

HTA Methods

Managing Uncertainty

10. Develop an agreed framework to ensure that health technology assessments aim to identify the **most likely or most plausible central estimate of health and outcomes** to form the base-case analysis, based on validated evidence. This should be stated explicitly in policy and methods guidelines.
11. For the purpose of demonstrating clinical superiority and cost effectiveness **when head to head trials are not available**, adopt the methodology accepted in other HTA markets (e.g. NICE, CADTH).

Comparator selection

12. The comparator should be the therapy(ies) **most likely to be replaced in clinical practice** by the new intervention, aligned with other HTA bodies and good HTA practice. This is consistent with the earlier interpretation of the National Health Act (pre-2015).
13. **Where there are multiple comparators,** the economic assessment should calculate a weighted average price for the new therapy based on the proportion of use that it replaces for each of the comparator therapies.
14. Explore ways to overcome issues facing medicines where the **clinically appropriate comparator has been commoditised**.

Real World Evidence

15. Adopt a high level, principles-based framework for **accepting and assessing RWE**.
16. Develop **standards for the utilisation of RWE** for post-marketing monitoring in the reimbursement context. This would require enhanced system infrastructure to **centralise linked health data** and provide appropriate access to stakeholders, including industry.

Transparency in Decision Making

17. Create a framework for **predictable, consistent and transparent incorporation of contextual factors**, such as patient and consumer input, severity of disease, equity, confidence in the evidence, assumptions and other relevant factors into HTA decision making.

Horizon Scanning

18. Co-develop and implement an **Horizon Scanning Roadmap**, detailing the steps all stakeholders must take to implement nationally coordinated horizon scanning, to deliver on the commitment in clause 6.2 in the Strategic Agreement.

Multi-Sponsor combination treatments

19. Seek **guidance from the ACCC on competition law** to enable discussion between multiple Sponsors at time of submission and PBS listing.

Q3 – Barriers to equitable access

Cell and Gene Therapies

20. Establish a **single HTA assessment body** for cell and gene therapies to remove current inconsistencies and complexities to streamline the pathway for patient access.
21. Establish a **single federal funding source** for the product costs of cell and gene therapies, similar to PBS funding of medicines.
22. Streamline and, where appropriate, **standardise the clinical delivery of cell and gene therapies** to ensure equitable patient access and improved quality of life for patients and autonomy for clinicians to best meet the needs of patients under their care.

Rare Disease Therapies

23. **Identify and track HTA applications for orphan drugs** through reimbursement pathways so that rare disease specific issues can be identified and addressed.
24. Coordinate HTA applications for rare disease therapies through a **single entry point within the DoHAC**.
25. Recognise in HTA guidelines that, for rare diseases, **observational data is the best evidence available** for decision making.
26. Implement a **direct and streamlined path to funding** via the Life Saving Drugs Program (LSDP).

Q4 – Elements that detract from person-centredness

27. Formulate a robust and formal framework for **earlier and more meaningful consumer engagement** across the lifecycle of a medicine, to deliver on clause 6.3 of the Strategic Agreement.
28. Provide greater transparency on the **utilisation of consumer evidence and how it informs decisions** made by HTA agencies.

Q7 – Reforms for consideration

A. Commit to delivering faster access for patients through policy and process reform, by:
    29. Ensuring all assessment and recommendation processes are aligned to allow for **reimbursement from TGA registration.**
    30. Introducing **interim funding** for certain medicines.
B. Reform the HTA system to better enable first time success through the PBAC process, by:
    31. Frontloading the system through **earlier engagement**, including patient involvement.
    32. **Streamlining the interactions** of the HTA Committees.
    33. Introducing an **independent price negotiation process** to expedite access for certain medicines, to be mutually agreed.

34. Expanding the current **independent review mechanism**, or considering an independent appeals process.
35. Ensuring there are **agreed, transparent metrics** for HTA processes to enable faster access.

C. In addition to the above recommendations, ensure Australia is a first launch country, by:

36. Establishing **innovation incentives**.
37. Exploring co-developed **international work sharing**.

Glossary of Terms

ABBREVIATION	MEANING
AAP	Autorisation d'acces precoce (early access authorisation)
ACCESS	Australia-Canada-Singapore-Switzerland-UK Consortium
AIHW	Australian Institute of Health and Welfare
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphocytic leukaemia
AMNOG	Arzneimittelmarkt-Neuordnungsgesetz (Pharmaceuticals Market Reorganisation Act)
ARTG	Australian Register of Therapeutic Goods
ASCVD	Atheroslcerotic cardiovascular disease
ASMR	Amélioration du Service Médical Rendu (Improvement of the Medical Service Rendered)
ATMP	Advanced Therapeutic Medicineal Product
ATAGI	Australian Technical Advisory Group on Immunisation
ATV	Added therapeutic value
BSS	Bio Sciences Section
CADTH	Canadian Agency for Drugs and Technologies in Health
CAR-T	Chimeric antigen receptor T-cell therapy
CDF	Cancer Drugs Fund
CEEU	Consumer Evidence and Engagement Unit
CIRS	Centre for Innovation in Regulatory Science
COR	Comparable overseas regulator
CV	Cardiovascular
DLBCL	Diffuse large B-cell lymphoma
DoHAC	Department of Health and Aged Care
EMA	European Medicines Association
EHR	Electronic health record
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration
FH	Familial hypercholesterolaemia
Govt	Government
HAS	Haute Autorite de Santé (French National Authority for Health)
HOR	House of Representatives
HPA	Hyperphenylalaninaemia
HPP	Health Products Portal
HST	Highly specific therapy
HTA	Health technology assessment
HTAB	Health technology assessment body
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
IHPA	Independent Hospital Pricing Authority
ILAP	Innovative Licensing and Access Pathway
IMF	Innovative Medicines Fund

ABBREVIATION	MEANING
ITC	Indirect treatment comparison
JA	Joint assessment
JBA	Jurisdictional Blood Committee
KPI	Key performance indicator
LABA	Long-acting beta agonist
LDL-C	Low-density lipoprotein cholesterol
LSDP	Life-Saving Drugs Program
MAP	Medicines Australia
MAP	Managed access program
MBS	Medicare Benefits Schedule
MES	Managed entry scheme
mHCC	Metastatic hepatocellular carcinoma
MSAC	Medical Services Advisory Committee
MSW	Medicines Status Website
NASWSI	New Active Substance Work-Sharing Initiative
NBA	National Blood Authority
NDIS	National Disability Insurance Scheme
NHRA	National Health Reform Agreement
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIP	National Immunisation Program
NITAG	National Immunization Technical Advisory Group
NMA	Network meta-analysis
NME	New medical entity
NSCLC	Non-small cell lung cancer
NZ	New Zealand
OHTA	Office of Health Technology Assessment
OS	Overall survival
PAG	Patient advocacy group
pALL	Paediatric acute lymphocytic leukaemia
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PKU	Phenylketonuria
PICO	Population, intervention, comparator, outcomes
PMAB	Prescription Medicines Authorisation Branch
PMBCL	Primary mediastinal large B cell lymphoma
PMDA	Pharmaceuticals and Medical Devices Agency
PSD	Public summary document
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RWE	Real-world evidence
SEB	Scientific Evaluation Branch
TFL	Transformed follicular lymphoma

ABBREVIATION	MEANING
TGA	Therapeutic Goods Administration
Tx	Treatment
UK	United Kingdom
US	United States
VMA	Vaccine market access
WTP	Willingness to pay

Q1 – Elements that are working effectively

There are features of the reimbursement system that are working effectively

Q1 Recommendations

1. The parallel process could be even more effective in reducing time to access by, for example, the **removal of the requirement for a TGA Delegate Overview at time of PBAC decision** (refer to the recommendations in Chapter 7).
2. Special pricing arrangements and confidential pricing for medicines **should be retained**.
3. **Transparency operates well in parts of the system but should be improved** to enhance predictability (refer to the recommendations in Chapter 2).

The following features should be retained and, in some cases, improved:

- Special pricing arrangements and confidential pricing
- Indication-based pricing
- Parallel processing
- Defined timelines
- PBS process improvements – streamlined pathways
- Flexibility in decision-making
- Transparency of process
- TGA reforms
- Patient and prescriber choice
- Deeds of agreement

Special pricing arrangements and confidential pricing

The ability to secure confidential pricing arrangements is essential for innovative medicines to be considered part of a global launch sequence and for their continued public funding in Australia. On the global stage, Australia is a small but pivotal market. As a reference pricing country for many other countries around the world, the value attributed to new medicines in Australia influences the value attributed to those same medicines internationally. The capacity within the Australian reimbursement system to have published and effective prices is a key feature that helps retain access to medicines in this country, while also supporting access in countries that reference-price to Australia. Without this

flexibility, it is highly likely that fewer medicines would be registered, launched and reimbursed in Australia because of the risk of impacting access elsewhere. Special pricing arrangements and confidential pricing for medicines should be retained. Nonetheless, Medicines Australia notes that the need for SPA's would be reduced if medicines were valued more reasonably as per the recommendations in this submission.

Indication-based pricing

The health technology assessment (HTA) system is based on the principle of establishing the cost-effectiveness of new medicines as compared with existing therapies. In Australia, applications to reimburse new medicines are submitted by indication, and each undergoes its own evaluation to establish cost-effectiveness of the new medicine by indication in its own right. This means that, in theory, it is possible to achieve a different price in second and subsequent indications than was attributed to the new medicine in the first reimbursed indication, based on the clinical evidence and economic analysis supporting each submission. This is a feature of the system that works effectively and should be preserved.

Parallel processing

Parallel processing of registration and reimbursement applications was introduced in Australia in 2011. This process allows reimbursement applications to be submitted while an application for registration is ongoing, requiring only that the TGA Delegate's overview be available prior to the designated PBAC meeting. An analysis conducted for MA[3] for the years 2018-2023, shows that the time from registration to reimbursement is significantly faster using the existing parallel processing pathway (***Table 1***).

Table 1. Comparison of time from registration to PBS listing via the standard and parallel pathways from 2018 to 2023 by economic approach

	Average, days	Median, days	Range, days
Ever CEAs (superior)			
Parallel pathway (N=61)	379	319	49–1076
Standard pathway (n=51)	669	586	163–2405
Initial CMA (non-inferior)			
Parallel pathway (N=70)	229	198	49–624
Standard pathway (N=39)	744	674	164–2233

While it is not clear that the reduction in time to reimbursement of new medicines can be attributed entirely to parallel processing, it has undoubtedly been a contributing factor to faster access in some circumstances that Australians benefit from. At a minimum, parallel processing in its current form

[3] Wonder Drug Consulting. Bespoke analysis of the MAESTrO database. Available from: https://maestrodatabase.com/

should be maintained. However, one of the shared goals of the Strategic Agreement between the Commonwealth and Medicines Australia is to reduce time to access for Australian patients so that they can access new health technologies as early as possible. To achieve this goal, Medicines Australia believes that further improvements could be made by, for example, earlier initiation of the HTA process to align with the TGA application, thereby removing the requirement for the PBAC to receive the TGA Delegate's overview. This proposal is discussed in more detail in Chapter 7.

Defined timelines

The current HTA system outlines clearly defined timelines for the process from the Intent to Apply to PBAC recommendation. While some elements of these are dependent on timely provision of information by either sponsor companies or the Department, having clear milestones helps to provide certainty for all stakeholders.

The post-PBAC processes are less clearly defined, particularly after a sponsor receives a positive recommendation from the PBAC and/or the MSAC to the time of listing. The streamlined pathways initiative (see the following section) introduced some timelines, however there are further efficiencies which could be introduced to reduce the time taken, including greater visibility of the process for Sponsors.

PBS process improvements – streamlined pathways

The previous Strategic Agreement between the Commonwealth and Medicines Australia included objectives to be addressed in PBS process improvement outcomes, with the overall aim of improving the efficiency, transparency and timeliness of the PBS listing processes. A revised pathways framework was introduced from July 2019 and extended in January 2021. It involved the creation of four different pricing pathways for positive PBAC recommendation and four different pathways for resubmissions, plus improvements to pre-submission meetings. The PBS process improvements included the development of key metrics throughout the two-stage process.

The metrics show that the different resubmission pathways are being utilised with almost 30% of resubmissions utilising the Early Re-entry Pathway, around 10% using the Early Resolution Pathway and less than 1% utilising the Facilitated Resolution Pathway.[4]

Flexibility in decision-making

The HTA system in Australia as it currently stands allows flexibility in some key health policy areas, particularly in hard-to-quantify areas. For example, the lack of a specified ICER threshold allows some

[4] Stage 1 and 2 PBS Process Improvements, 2021-2022 Metrics report, https://www.pbs.gov.au/general/process-improvements/Stage-1-and-2-PBS-Process-Improvements-metrics-report-2021-22.pdf

flexibility in PBAC decision-making, meaning that the PBAC can incorporate less quantifiable factors such as high clinical need or the rarity of a condition into deliberations about the cost-effectiveness of a medicine. This can be observed in the ICERs accepted for medicines for rare conditions with small patient populations, which tend to be higher than for more common, chronic conditions. Retaining this flexibility as a feature of the Australian system is highly desirable.

However, flexibility in decision-making in isolation is not sufficient to ensure that access to medicines occurs as quickly as possible. Flexibility should be allowed for more than simply medicines for rare diseases or those with high added therapeutic value. This is discussed in more detail in Chapter 2.1

Transparency of process

Transparency promotes accountability and provides information for citizens about what their government is doing. In the case of the HTA of medicines, transparency allows the judgments made by HTA bodies to be assessed with regards to alignment with public policy and interests. Increasing transparency in HTA decision-making also improves the predictability of submission outcomes, reducing the risk of rejection and the need for resubmission, thus expediting access.

Much of Australia's HTA system is considered sufficiently transparent and works effectively. The processes are standardised and published, as are submission guidelines. An account of PBAC meeting discussions is provided in Public Summary Documents, and the process has clear timelines. However, there are key areas where transparency should be improved. These are discussed in detail in Chapter 2.2.

TGA reforms

The TGA reforms, introduced over a three year period from 2016, have significantly improved time to regulatory approval for certain medicines. The reforms included:

- Increased flexibility in pre-market assessment processes including expedited and provisional approval;
- A faster process for priority evaluation;
- Provisions to enable earlier data sets to be considered for provisional evaluation;
- Increasing use of assessments from comparable overseas regulators (such as the US and EU); and
- Changes to the regulation of complementary medicines.

In 2021-22, the mean and median approval times for the priority pathway were 136 days and 141 respectively and, for priority pathways, 102 and 65 days respectively. The latter was almost 60 days shorter than the mean approval time for the standard pathway and almost 100 days shorter than the mean approval time for the standard pathway.[5] In order to fully leverage this improvement and deliver

[5] Therapeutic Goods Administration. Performance Report 2021-22, p45

faster access for patients, it will be important for the HTA Review to deliver reforms which also speed up the reimbursement process.

Patient and prescriber choice

The PBS is an 'all comers' scheme, enabling the listing of multiple brands of a medicine, where these are available. This allows for patient and prescriber choice and also for competition, in F2, which brings the price down. Another positive feature is that the second and subsequent brands to market are able to list at the same price as the original brand.

Deeds of Agreement

A Deed of Agreement between the Department of Health and Aged Care and a Sponsor manages the effective price through an agreed rebate. The regulation and consistency in application of deeds of agreement is welcome. However, the agreed rebate is established at the initiation of the Deed and is reflective of a point in time; a percentage of Government expenditure to reflect an agreed effective price, generally for a term of 5 years. During a 5-year agreement, there are multiple changes that can occur to the determination of Government expenditure (e.g. changes in mark-ups and patient co-payments) and estimated patient utilisation that impacts the rebate calculation. Change can impact the effective price. Given the importance of a Deed to manage pricing outcomes, the Deed of Agreement process could be improved to ensure the process and mechanism reflects the agreed effective price. Processes should consider the duration of the Deed (generally 5 years), healthcare system reforms that can occur within the time of the Deed (e.g. Government initiatives to reduce the General Co-Payment to $30 per prescription) and evolution of patient utilisation over the period of the Deed.

Q2 – Barriers to earliest possible access

Measuring the patient access gap

The shared goals set out at clause 5.1 of the Strategic Agreement are:

- reducing time to access for Australians so that they can access new health technologies as early as possible
- maintaining the attractiveness of Australia as a first launch country to build on Australia's status as a world leader in providing access to affordable healthcare.

To achieve these goals, medicines must be submitted to the TGA as soon as possible after the first global submission, and publicly funded immediately, or as soon as possible, once TGA registration is achieved.

In fact, less than half (44%) of new molecular entities (NMEs) registered in Australia between 2016-2021 went on to be reimbursed, compared with 96% in Japan, 84% in Germany, 80% in the UK and 62% in France. In real numbers, Australia had just 74 of registered NMEs reimbursed, less than half that in Germany (165), Japan (154) and the UK (151)[6].

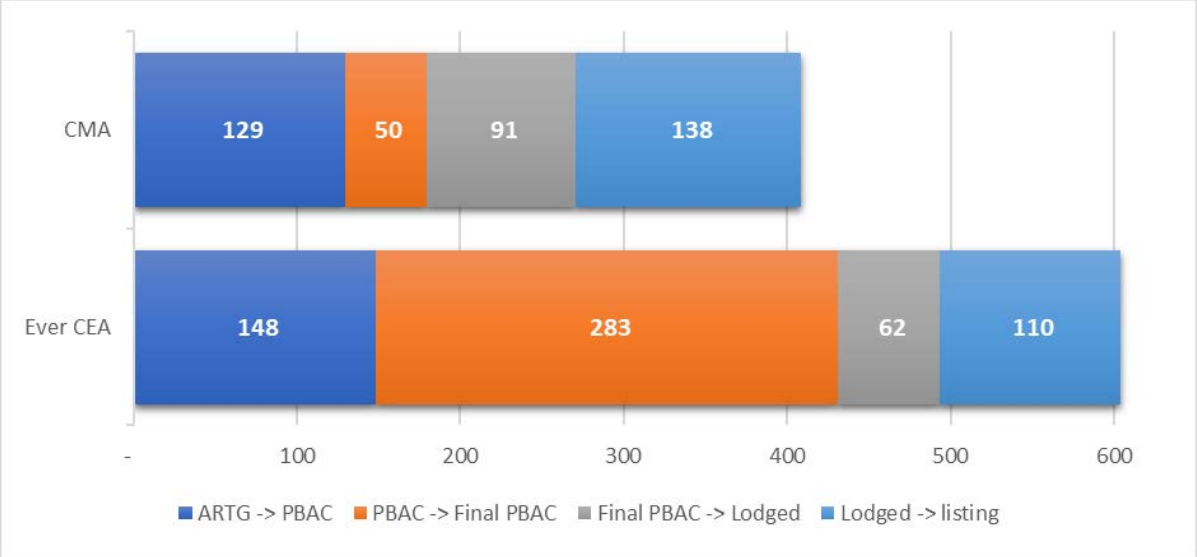
For those innovative, first indication medicines that are funded in Australia the average time from local regulatory registration to public funding was most recently reported as 466 days[7], much longer than other OECD countries such as Germany, France, Japan, the UK, Switzerland, Norway, Sweden, Finland and Austria.

The current Australian system provides reimbursed access to patients only after a full HTA is complete and a final price has been negotiated. In theory, reimbursed access can be achieved within approximately 60 days of TGA registration if: there is parallel processing; a first time PBAC recommendation; and no delays to post-PBAC negotiations. In practice, however, there are very few cases where this is achieved. Ideally, funding would be available at the point where new medicines/new uses for existing medicines are deemed safe and effective in Australia by the TGA and entered on the ARTG. Delays in time between ARTG entry and PBS listing has been coined the 'patient access gap'.

[6] Medicines Australia. Medicines Matter: Australia's Access to Medicines 2016-2021. Australia: Medicines Australia; 2022. Available from: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2023/04/Medicines-Matter-2022-FINAL.pdf
[7] Ibid

An analysis of PBAC recommendations, between March 2021 and March 2022, leading to PBS listing indicated that 'ever' cost-effective submissions (where cost-effectiveness was utilised in at least one of the submissions leading to the listing) had a mean patient access gap of approximately 600 days[8]. Updating this analysis to include PBAC recommendations until March 2023 (including listings as of 6 May 2023) results in a similar time to listing of 603 days. For listings based on cost-minimisation (typically implying no incremental cost to Government) the mean patient access gap was 408 days (***Figure 1***). Cost-effectiveness analyses are typically used where the new medicine is considered to offer superior health outcomes over current care. It is therefore a concern that the therapies that are likely to provide the most benefit to patients take the longest to be funded. Incremental reforms over time have helped to reduce the patient access gap such as the introduction of parallel TGA/PBAC processing in 2011, and early re-entry pathways in 2021. However, 603 days is a substantial delay and Australia ranks well behind other markets in terms of time to reimbursed access.

Figure 1: Patient access gap (days) March 2021 to March 2023*



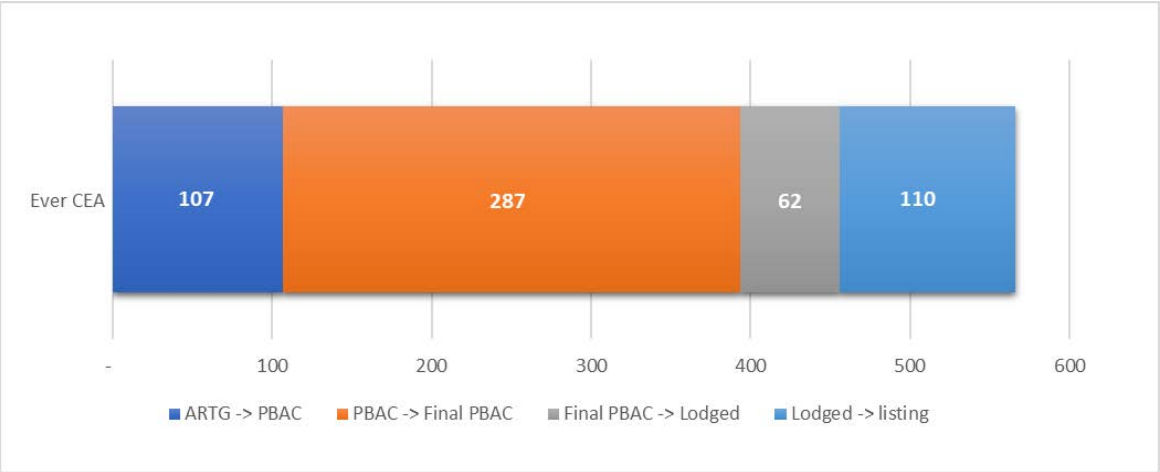
**PBAC recommendations leading to listings as of 31 May 2023*

For ever-CEA cases, the time between the first PBAC meeting at which a submission was considered and the final PBAC meeting at which a positive recommendation was given represented approximately 40% of the time comprising the patient access gap, with the remaining 60% evenly split between the time from ARTG entry to the first PBAC meeting and post-PBAC listing activities.

For ever-CEA cases, the mean time between ARTG entry and the first PBAC meeting was skewed by one outlier (2,131 days). Removing this case shows that, for most listings, the patient access gap is being driven by resubmissions to the PBAC and the post-PBAC listing process (***Figure 2)***.

[8] Millar, D, Commercial Eyes Analysis. Presentation by Douglas Millar at ARCS 2022 Conference, ARCS, Australia; 2022.

Figure 2: Patient access gap (days) March 2021 to March 2023 with outlier removed



**PBAC recommendations leading to listings as of 31 May 2023*

The issue of 'resubmission churn'

Resubmissions remain the greatest driver of delayed access for therapies with a claim of superiority to current treatment. Between 1 July 2021 and 30 June 2022, only 4 out of 37 (11%) submissions seeking a higher price over the existing alternative(s) were recommended first time[9]. Approximately 60% of the resubmissions during this time passed via the standard resubmission pathway (a full resubmission), which is used when the PBAC considers that the remaining issues cannot be easily resolved. Typically, such resubmissions include significant re-writing of both the clinical and economic sections of the original submission and may require additional literature reviews, indirect comparative analyses, subgroup analyses or other research. This new information is then assessed by the evaluators, sub-committees and PBAC. This is therefore a very resource intensive exercise for both the Sponsor and the Department, and incurs a delay to access for patients of at least 8 months (given the frequency of PBAC meetings and the standard process timeline). Sponsors pay for this process through cost recovery fees but an additional consideration is the utilisation of specialist person-hours in the Department and evaluation teams to complete the re-evaluation. Gaining as much alignment as possible on the decision problem and analytical approach at an early stage of the HTA process is expected to be considerably more efficient than addressing these issues via full resubmissions, and on average would reduce the time to access.

Issues addressed in this chapter

The patient access gap and resubmission churn arise from a range of policy, method and other issues which are explored in detail in this chapter, as follows:

[9] Pharmaceutical Benefits Scheme. STAGE 1 and 2 PBS PROCESS IMPROVEMENTS 2021-22 Metrics Report. Australia: PBS; 2023. Available from: https://www.pbs.gov.au/general/process-improvements/Stage-1-and-2-PBS-Process-Improvements-metrics-report-2021-22.pdf

2.1 HTA Policies

- Willingness to invest in medicines
- Defining Time to Access
- Broadening the value of medicines
- Lowering the discount rate

2.2 HTA Methods

- Managing uncertainty
- Comparator selection
- Real world evidence
- Transparency in decision making

2.3 Horizon Scanning

2.4 Multi-sponsor combination treatments

2.5 Interaction with Evaluators

2.1 HTA Policies

Willingness to invest in medicines

Q2 Recommendations – Willingness to invest in medicines

4. While the PBAC should retain flexibility in the application of ICER thresholds, **willingness to invest in medicines warrants higher ICER ranges**, which the PBAC should be willing to recommend. The ICER ranges should then be tracked and published by the Government across broad disease areas and clinical settings.

A key aspect which should be considered as part of the HTA review is the Australian Government's willingness to invest in medicines as represented by the range of ICERs which the PBAC accepts when recommending medicines for PBS listing.

An ICER represents what society is willing to pay for health gains, hence its assumed value is important. The ICERs accepted for innovative medicines in Australia should reflect its standing as a highly developed country, which would enable more patients to access the medicines they need.

The acceptable range for the ICER in Australia, in general, is understood to be up to approximately A$45,000–A$75,000 per QALY, although this is not formally documented in the PBAC guidelines. The PBAC does have discretion to recommend applications with ICERs above and below this range, with consideration of other factors (**Table 2**).

Table 2: Quantitative and qualitative factors that may influence PBAC recommendations

Quantitative	Qualitative
• Comparative health gain • Comparative cost-effectiveness • Patient affordability in the absence of PBS subsidy • Predicted use in practice • Financial implications for the PBS • Financial implications for the Australian government health budget	• Overall confidence in evidence and assumptions in submission • Equity • Presence of effective therapeutic alternatives • Severity of medical condition treated • Ability to target therapy with the proposed medicine precisely and effectively to patients likely to benefit most • Public health issues • Any other relevant factor

Source: PBAC[10]*.*

PSDs, which provide an overview of the key considerations and drivers for the PBAC's decisions, suggest that an ICER as high as A$200,000 may be acceptable for rare diseases where there is a high and acute unmet need, and as low as A$15,000 for vaccines, due to the uncertainty of the value of broad, preventative public health interventions.

Case Study: Meningococcal B vaccine (4CMenB/Bexsero)

Invasive meningococcal disease is a devastating condition that can escalate quickly, leading to death or severe disability. Vaccination against A, C, W and Y strains is part of the standard childhood NIP; however, most Australian children remain unprotected against Meningococcal B. The PBAC considered 4CmenB four times between November 2013 and November 2019, rejecting it each time on the grounds of lack of cost-effectiveness. Ultimately, in November 2019, with the provision of additional evidence from the Sponsor, the PBAC approved 4CmenB for a small, high-risk population.[11] It has been listed on the NIP for Aboriginal and Torres Strait Islander children since July 2020. A key factor in this determination was a low accepted ICER to reflect the opportunity cost of investing in a vaccine or public health intervention. Rather than the $45,000-$75,000 per QALY used for medicines, the accepted ICER was set at only $15,000 per QALY.

[10] Pharmaceutical Benefits Scheme. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee Version 5.0. Australia: PBS; 2016. Available from: https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf

[11] Pharmaceutical Benefits Scheme. Public Summary Document: MULTICOMPONENT MENINGOCOCCAL GROUP B VACCINE. Australia: Australian Government; 2019. Available from: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-11/files/multicomponent-meningococcal-b-vaccine-psd-november-2019.pdf

Case Study: Evolocumab

Evolocumab is listed on the PBS for patients with familial hypercholesterolaemia (FH) and patients without FH who have high-risk symptomatic atherosclerotic disease (ASCVD). Elevated LDL-C, the primary component of total cholesterol, causes ASCVD and is a principal driver of cardiovascular (CV) risk in humans[12]. CV disease is one of Australia's largest health problems and consequences of CV events include death, hospitalisation, disability, and an increased risk for subsequent more serious and costly CV events[13] (Danese et al. 2016). PBAC in its decision-making for evolocumab has progressively set lower acceptable ICERs as the PBS listing has been expanded. For example, an ICER of $30,000 was set to establish listing of evolocumab in patients with high-risk ASCVD with LDL-C > 2.6 mmol/L (at the November 2019 PBAC meeting). A lower ICER of $25,000 was set for the same ASCVD population with LDL-C between 1.8 and 2.6 mmol/L (at the July 2022 PBAC meeting). In all instances, the outcome being prevented, and hence valued, is the same – a reduction in serious CV events and death.

Case Study: Romosozumab

Osteoporosis is a serious, chronic condition with no cure that affects mostly elderly Australians. The consequences of osteoporotic fractures can be debilitating and may lead to significant morbidity, loss of independence and mortality. An initial course of a bone-forming therapy, such as romosozumab, is recognised as the best treatment option for patients with low bone density presenting for treatment having already experienced a very severe fracture or multiple fractures and who consequently are at a highly elevated risk of fracturing again in the next 1 to 2 years[14]. Australian patients cannot currently access first-line bone-forming therapy on the PBS. The PBAC considered romosozumab five times between 2018 and 2023. Initially, it was recommended only for second-line use, and listed in 2021 on a cost-minimisation basis versus an existing bone forming therapy (March 2020 PBAC meeting). Following two additional submissions, romosozumab was recommended for first-line use at the March 2023 PBAC meeting. The PBAC has set the ICER at $37,915 for this listing with no rationale provided as to why a relatively low valuation was applied to a serious disease in a vulnerable population.

[12] Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European heart journal 2017;38(32):2459-2472.
[13] Danese MD, Gleeson M, Kutikova L, et al. Estimating the economic burden of cardiovascular events in patients receiving lipid-modifying therapy in the UK. BMJ open 2016;6(8):e011805.

[14] Gehlbach S et al. Previous fractures at multiple sites increase the risk for subsequent fractures: the Global Longitudinal Study of Osteoporosis in Women. J Bone Miner Res. 2012;27:645-653.

While there is no universal agreement on the appropriate ICER value, when considering revised ICERs for Australia, it is important to note that the currently accepted ICERs:

- Have not kept pace with inflation
- Are below international recommendations based on GDP/capita.
- Place a lower value on a life and health outcomes than those used by other government departments. (The Department of Prime Minister & Cabinet's Office of Best Practice Regulation states that "Based on international and Australian research a credible estimate of the value of a statistical life is $5.3m and the value of statistical life year is $227,000 in 2022 dollars".)

The PBAC should retain the flexibility to accept variable ICERs while acknowledging that a higher willingness to pay would allow patients faster access to innovative medicines.

Defining time to access

Q2 Recommendations – Defining time to access

5. There should be **agreement from all parties** that time to patient access for medicines means the time from when an innovative medical technology (including medicines, biotherapeutics and vaccines) is registered with the TGA to when it becomes available to patients on the PBS.
6. The Department of Health and Aged Care should introduce integrated and agreed data metrics and a **comprehensive system for measuring the time to patient access**, and report publicly in line with the National Medicines Policy.

There are two quite different narratives about the patient access gap in Australia. Medicines Australia considers the Australian patient access gap to be the time from when an innovative medical technology (including medicines, biotherapeutics and vaccines) is entered on the ARTG to when it becomes available to patients on the PBS. It annually commissions a report to assess the timelines for registration and reimbursement of new medicines for Australian patients, against other OECD countries. Industry's narrative about the patient access gap is based on this and other reports.

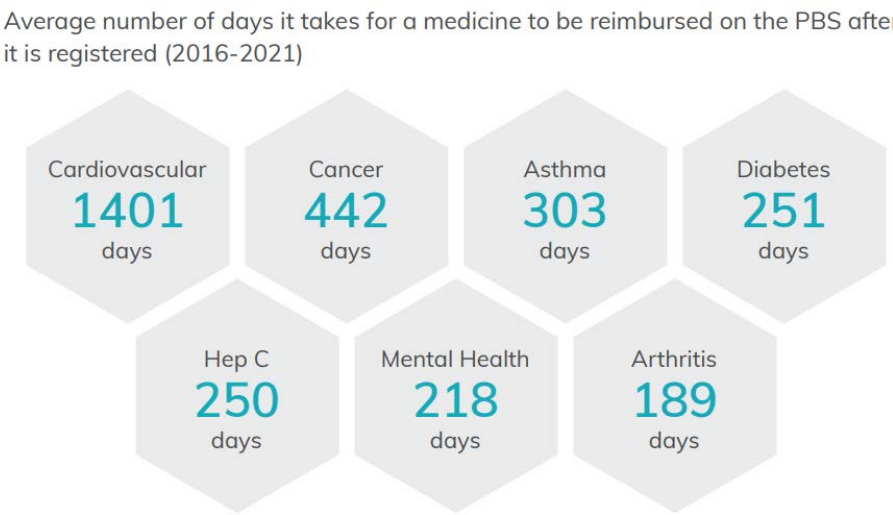
The latest Medicines Matter report[15] finds that:

1. From 2016 to 2021, Australia ranked 16th out of 20 for the number of reimbursed NMEs, an increase of one place compared with the previous Medicines Matter report.

[15] Medicines Australia. Medicines Matter: Australia's Access to Medicines 2016-2021. Australia: Medicines Australia; 2022. (Showing time to listing for first indication of an NME anywhere in world.) Available from: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2023/04/Medicines-Matter-2022-FINAL.pdf

2. Australia has remained in 15th position out of 20 for the proportion of reimbursed NMEs, 9% below the OECD average.
3. The top four OECD countries reimbursed more than 70% of NMEs in less than 6 months from registration, while only 17% of NMEs were reimbursed in Australia in less than 6 months.
4. The average time from registration to reimbursement for all 20 OECD countries has increased to 384 days, with Australia's average at 466 days. This means Australian patients are waiting months longer for new medicines to become available on the PBS.
5. NME registration to reimbursement timeframes vary significantly between therapeutic areas.

Figure 3: Average number of days it takes for a medicines to be reimbursed on the PBS after it is registered (2016-2021)



Multiple resubmissions for reimbursement applications are the biggest contributor to the patient access gap in Australia. An analysis of medicines that were recommended by the PBAC in the year to March 2022 took approximately 600 days (on average) to be approved. Each medicine required multiple submissions.[16]

Industry's narrative has been supported by numerous patient groups, whose submissions to the *Inquiry into approval processes for new drugs and novel medical technologies in Australia*, all raised the issue of delays in time to access.

[16] Millar, D, Commercial Eyes Analysis. Presentation by Douglas Millar at ARCS 2022 Conference, ARCS, Australia; 2022.

The DoHAC's narrative about the patient access gap can be gleaned from its submission to the same Inquiry, and the most recent CIRS R&D briefing.[17] Contained in these documents are some of the following comments:

- "However, the CIRS report found significant delays in companies bringing new medicines to Australia. In the CIRS study, 84% of the new medicine approvals surveyed in 2019 were approved by FDA, EMA, PMDA, Health Canada or Swissmedic before being approved by the TGA. The median 'submission gap' between the first regulatory submission to the US FDA and regulatory submission and approval by the TGA was 535 days."
- "The CIRS report showed that where 'parallel processing' of regulatory and reimbursement submissions is sought the delay between the two was a matter of weeks. Australia had the shortest overall median time between regulatory approval and health technology assessment (HTA) recommendation, suggesting the proactive approach within Australia to move toward synchronising the timing of HTA and regulatory recommendation is achieving its purpose, " and
- "Australia had the fastest median rollout time from regulatory submission to the first HTA recommendation in 2021 (403 days), followed by Canada and Germany (562 and 563 days, respectively)".

These competing narratives cannot be reconciled unless and until the Government introduces a systematic approach to measuring time to access, from registration to listing. Nor can the HTA system be properly held to account without proper measurement.

The New Frontier Report made a number of recommendations around the need to measure outcomes. Among other things, it recommended that:

> *The Department of Health publish data on application processing times and positive recommendation rates for the Pharmaceutical Benefits Advisory Committee and other Health Technology Assessment bodies.*
>
> *The Department of Health should publish Health Technology Assessment processing times annually, benchmarked against other nations with advanced HTA processes.*

The *Strategic Agreement (2022-2027)* under clause 13.2.2 and Appendix 3 states that the Department of Health and Medicines Australia agree to work collaboratively to determine a range of key

[17] Note that CIRS report focusses on time to PBAC recommendation, not time to PBS listing.

Centre for Innovation in Regulatory Science. Review of HTA outcomes and timelines in Australia, Canada and Europe 2017-2021, CIRS R&D Briefing 86. UK: CIRS; 2022. Available from: https://cirsci.org/publications/cirs-rd-briefing-86-hta-outcomes-in-australia-canada-and-europe-2017-2021/

performance indicators (KPI) for reporting during the term of agreement[18]. The main measurement is around reducing time to listing, and seeks to understand what measures are within industry's control and what measures are within Government's control.

The introduction of metrics to understand time to access is a critical element for assessing whether the HTA system delivers the earliest possible access for Australian patients. It should be a priority for the Department of Health.

Broadening the valuation of medicines

Q2 Recommendations – Broadening the valuation of medicines

7. **Broaden the HTA valuation** from a direct health sector patient perspective to include a health and welfare patient and carer perspective, including those with a direct (and indirect) impact on the Australian Government budget.
8. Develop agreed criteria for situations where **second-order effects** on patients and their caregivers, such as social welfare and carer impacts, should be included in the HTA assessment process, including workable methodologies for the **transparent inclusion of second order effects** or patient benefits , in a way that supports equity of access.

The narrow valuation of medicines under the current HTA assessment process can result in medicines being unable to secure reimbursement, and represents a current and future barrier to earliest possible access. As demonstrated by the approach to COVID-19, the wider benefits of new medicines and vaccines are valued by the Australian Government and community. Increasingly, it is being recognised that benefits to health have flow-on benefits to productivity, capacity to contribute to the economy, and less reliance on other parts of the healthcare system and social welfare. However, the HTA assessment process does not recognise these wider benefits.

The PBAC and MSAC take a health budget perspective, capturing direct benefits to the patient and direct costs to the health budget. While Sponsors can and do bring some analysis of these wider benefits (sometimes called 'second-order effects' or 'societal perspective'), the PBAC Guidelines relegate this to a supplemental analysis, and it is not given much weight because the primary focus is on the health and/or PBS/MBS budgets. In practice, there is inconsistency in how these benefits and costs are accepted and important wider indirect benefits and costs to the patient, their families and carers, and other Government budgets are largely disregarded.

[18] Medicines Australia, Australia Department of Health. Strategic Agreement in relation to reimbursement, health technology assessment and other matters. Australia: Medicines Australia; 2022. Available from: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2021/09/Medicines-Australia-Strategic-Agreement-2022-2027.pdf

Benefits that are often excluded from the calculation of cost-effectiveness include social welfare impacts, carer impacts, National Disability Insurance Scheme (NDIS) impacts, benefits valued by patients which are not currently captured because they are outside the clinical trial settings, productivity gains and tax revenue. There are currently no standard methods for estimating indirect cost and benefits in economic evaluations in Australia; however, internationally there are other payers that use a societal perspective.

Case Study: Consideration of broader effects in an economic model

An example of a submission where broader effects were included in the modelling but not accepted by the PBAC is siponimod (November 2019):

> *"6.40 The BAC-MS study collected data from participants' National Disability Insurance Scheme (NDIS) plans, which were included in the model. The PBAC has not previously considered NDIS costs. The ESC considered that these costs should not be considered as part of the base case because of the low sample numbers in BAC-MS and the uncertainty around the costs reported in the NDIS plans versus the actual expenditure incurred."*

The submission was ultimately rejected.

Improved health can deliver increased economic and standard-of-living outcomes. The Australian Government's Office of the Chief Scientist[19] estimates that, if a 10% health improvement were applied to the entire working age population (18 to 69 years), the expected change in GDP would be around 0.216%, or $2,801 million.

There is a growing body of evidence around the non-health benefits that medicines deliver, as well as the impact on State hospital budgets:

- Health strategies for Australians living with osteoarthritis can help recover $1.9 billion in lost super from early retirement and return $3.9 billion to the economy[20]
- The introduction of new treatments for multiple sclerosis (MS) has significantly reduced the economic burden from lost wages over the past 7 years – from 49% to 32%[21]

[16] Australian Government Office of the Chief Scientist. The importance of advanced biological sciences to the Australian economy. Australia: Australian Government; 2016.Available from: https://www.science.org.au/files/userfiles/about/biology%20report_web.pdf

[20] Schofield D, Shrestha R, Cunich M, West S. Measuring labour productivity and the benefits of interventions for osteoarthritis. Sydney: Medicines Australia. 2016 Sep 2. Available from: https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2019/08/20160905-rpt-FINAL-Schofield-OA_productivity-final-report.pdf

[21] UTAS, Menzies Institute for Medical Research. Health Economic Impact of Multiple Sclerosis in Australia in 2017. Australia: MS Research Australia; 2018. Available from: https://www.msaustralia.org.au/wp-content/uploads/2018/08/executive-summary_health-economic-impact-of-ms-in-australia-in-2017-report_ms-research-australia.pdf

- The cost of early retirements due to ill health on GDP was estimated to be $45.3 billion in 2017 and expected to increase to $53.4 billion in 2025. Effective health programs, such as listing of new medicines, can reduce these costs by up to 20%[22]
- COVID-19 vaccines are estimated to have reduced the impact of the pandemic on the economy to an estimated $214 billion, resulting in a positive incremental benefit of $181 billion.[23]

Other HTA agencies such as those in the UK, Canada and the Netherlands include caregiver or family member utility in their guidelines and methods for HTA. In Australia, these are only considered as a scenario analysis in limited circumstances.

Table 3: Caregiver and Family Member Utility in selected HTA Agencies (adapted from Basarir et al.[24])

HTA Agency	Statements from Methods Guide	Base case/ scenario
NICE (England)	Perspective on outcomes: all direct health effects, whether for patients or, when relevant, carers	Base case
CADTH (Canada)	Target population may include patients and their informal carers (i.e. unpaid carers). Researchers should consider any potential spillover impacts (such as due to changes in the level of care required by patients beyond those individuals for whom the interventions are being targeted).	Base case if carer is considered part of the target population
ZiN (Netherlands)	Economic evaluation is carried out and reported from the societal perspective. All relevant societal costs and benefits, irrespective of who bears the costs or to whom the benefits go, should be taken into account in the evaluation and reporting	Base case

As a first step, the HTA valuation should be broadened from a direct health sector patient perspective to include a health and welfare patient/carer perspective, including those with a direct impact on the Australian Government budget. This would take into account the costs and benefits affecting the

[22] The McKell Institute. Our Health Our Wealth, The Impact of Ill Health on Retirement Savings in Australia. Australia: Medicines Australia; 2018. Available from: https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2018/09/Our-Health-Our-Wealth-full-report.pdf

[23] Fox, N.; Adams, P.; Grainger, D.; Herz, J.; Austin, C. The Value of Vaccines: A Tale of Two Parts. Vaccines **2022**, 10, 2057. https://doi.org/10.3390/vaccines10122057

[24] Basarir H, Brockbank J, Knight C, Wolowacz. The Inclusion of Utility Values for Carers and Family Members in HTAs: A Case Study of Recent NICE Appraisals in the UK. UK: RTI Health Solutions; 2019. Available from: https://www.rtihs.org/sites/default/files/29662%20Basarir%202019%20The%20inclusion%20of%20the%20utility%20values%20for%20carers%20and%20family%20members%20in%20HTAs%20a%20case%20study%20of%20recent%20NICE%20appraisals%20in%20the%20UK.pdf

patient and their carers and dependents. This needs to occur as the base-case economic analysis (Section 3 of the PBAC submission), not as a supplementary analysis (Section 5).

Within a PBAC submission, the perspective taken in Section 4 (budget impact) should be aligned with that of Section 3 (cost-effectiveness). Currently, the Section 4 budget impact estimates are limited in scope to direct Federal health costs (PBS/MBS). This means that the true cost to government is never illuminated and does not consider the savings generated to other State and Federal Government portfolios. It is proposed that an acceptable method is agreed to calculate the true net cost of a new PBS listing when being considered by the Departments of Finance and Treasury. This would include costs associated with the Federal health and welfare portfolios as well as State health portfolios and shared agreements (e.g. the NHRA).

As a second step, agreed criteria could be developed for situations where second-order effects on patients and their caregivers should be included in the HTA assessment process. For example:

- High-priority medical conditions
- Conditions that have a direct and substantial impact on caregivers (and consequently society)
- Conditions that affect patient productivity
- Treatments that have a measurable impact on carers and patient productivity.

If a new medical technology meets these conditions, the indirect costs and benefits should be included in the base-case economic evaluation. Workable methodologies for the transparent inclusion of second-order effects or patient benefits in the HTA assessment process would need to be developed.

Lowering the discount rate

Q2 Recommendations – Lowering the discount rate

9. **Lower Australia's discount rate in line with international best practice** to recognise the value of preventative treatments and cures, and speed up access to them.

As part of the Strategic Agreement between Medicines Australia and the Commonwealth, Medicines Australia made a submission[25] to the PBAC on the base-case discount rate, in which it was recommended that the discount rate should be lowered from 5% to 1.5%. The PBAC subsequently acknowledged that Australia's discount rate could be lowered to between 3.5% and 4% to bring the country closer to other recommended international standards, recommending that the issue be considered in the HTA Review.

[25] Medicines Australia. Submission to the PBAC on the Base Case Discount Rate. Australia: Medicines Australia; 2022. Available from: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2022/02/Medicines-Australia-submission-to-PBAC-Discount-Rate-Submission-January-2022.pdf

Discount rates reflect how society values future outcomes compared to present outcomes. Many medicines, vaccines and treatments provide long-term health benefits. For example, a child receiving a polio vaccine will reap the benefits of that vaccine for the rest of their life. On the other hand, a new cancer treatment may increase someone's survival rate by 5 years. The value of treatments that have a long-term or lifelong benefit continue to be discounted over the entire period for which it benefits patients, while those that have a shorter-term benefit (such as cancer treatments) are only discounted for the shorter period of time for which they benefit patients, which means that the medicine with longer-term benefits is not valued as highly. The PBAC set the base discount rate at 5% in 1990 with reference to Canada. Since that time, this discount rate hasn't changed, despite other international countries (including Canada and England), recommending lower base discount rates to make way for more preventative and curable medicines, vaccines and treatments.

Our society and values have changed since 1990 and there is an increasing recognition of the importance of preventative healthcare. The COVID-19 vaccine rollout is just one example of the importance of preventative therapies. If left unchanged, the discount rate will risk significantly reducing patient access to cutting edge therapies and affecting the long-term future health of generations of Australians, particularly young people who stand to benefit the most from preventative medicines early in their life. In Australia, the 5% discount rate has contributed to delays in accessing vital therapies, including vaccines for human papilloma virus (HPV) in adolescents, meningococcal disease in children and adolescents, zoster virus for 60-year-olds and adolescents.

Table 4: Discount rates around the globe

The recommendation in this section is based on a review of international HTA discount rate practice, the impact of high discount rates on access to medicines, and government policies which stress the importance of long-term health, such as Australia's *Long-Term National Health Plan*. A lower discount rate of 1.5% will recognise the value of long-term future health benefits and:

- Prove to the Australian people and the world that our population's future health is valued
- Contribute to improving the speed of patient access to new and innovative therapies
- Promote PBAC decision making equity
- Align with the Commonwealth Government's preventative health agenda.

2.2 HTA Methods

Managing Uncertainty

Q2 Recommendations – Managing uncertainty

10. Develop an agreed framework to ensure that health technology assessments aim to identify the **most likely or most plausible central estimate of health and outcomes** to form the base-case analysis, based on validated evidence. This should be stated explicitly in policy and methods guidelines.
11. For the purpose of demonstrating clinical superiority and cost effectiveness **when head to head trials are not available**, adopt the methodology accepted in other HTA markets (e.g. NICE, CADTH).

Between 1 July 2021 and 30 June 2022, only 4 out of 37 (11%) submissions seeking a higher price over the existing alternative(s) were recommended the first time[26]. This high rate of first-time rejections is the principal driver of delay to access for therapies that are superior to current treatment. These are the therapies that patients most urgently need access to.

Between March 2021 and March 2022 62 major/Category1/Category 2 submissions were rejected by the PBAC. In the PBAC's outcomes statements, uncertainty in the ICER or magnitude of benefit was mentioned in 37 (60%) of the cases[27].

Uncertainty is inherent in HTA. However, the PBAC frequently proposes respecification of economic models and interprets clinical data in ways that result in an unrealistically conservative estimate of the benefits of new medicines. This has been interpreted as a combination of a) the PBAC having a low tolerance for risk and using conservative assumptions as a risk mitigation strategy, and b) applying conservative assumptions as part of a price negotiation process. In either case, the application of conservative assumptions obfuscates the unbiased assessment of the most plausible central estimate of clinical and economic outcomes, leading to a less transparent, less efficient process, and delayed access. In the case of a standard resubmission, access is delayed by at least 8 months and some cases involve multiple resubmissions. Additionally, future submissions may be affected because the assumptions in the prior submission set a precedent for future evaluations. Lastly, conservative assumptions combined with already relatively low ICERs compound to reduce the attractiveness of Australia as a first launch country. The issue manifests in the following ways.

[26] Pharmaceutical Benefits Scheme. STAGE 1 and 2 PBS PROCESS IMPROVEMENTS 2021-22 Metrics Report. Australia: PBS; 2023. Available from: https://www.pbs.gov.au/general/process-improvements/Stage-1-and-2-PBS-Process-Improvements-metrics-report-2021-22.pdf

[27] Millar, D, Commercial Eyes Analysis. Presentation by Douglas Millar at ARCS 2022 Conference, ARCS, Australia; 2022.

A conservative approach to translating clinical outcomes to economic modelling and a conservative view of long-term outcomes

Evaluations and considerations are often inconsistent with the PBAC guidelines or with accepted academic best practice. For example, the use of truncated time horizons, artificial waning of treatment effect, and forced convergence of modelled outcomes are frequently requested. When combined, the result is an unsupported and clinically implausible estimate which significantly undervalues the additional benefit therapies offer (i.e. incremental QALY gain).

Limited acceptance of HEOR analysis methods

Whilst the PBAC Guidelines allow the use of tools such as indirect treatment comparisons (ITCs) and network meta-analyses (NMAs) for any submission, they are generally accepted only when a cost-minimisation approach is taken rather than to support a claim of clinical superiority and cost-effectiveness. This has become an increasingly challenging paradigm over the past 10 years and will impact medicines access in the future. An example of why this is problematic is outlined below.

Scenario: The challenging paradigm

- PBAC rejects a new therapy for reimbursement (medicine "A") and it is not available to patients.
- The next innovation (medicine "B") enters Australia – its RCT evidence has used medicine "A" as its comparator; however, this doesn't reflect Australian clinical practice where medicine "A" is not used.
- Because medicine "B" has used a different comparator from what is locally available, the sponsor of medicine "B" must perform an ITC with the locally used medicine in its cost effectiveness submission – something which the PBAC does not accept routinely.
- Medicine "B" is rejected on the basis of uncertainty, which is inherent in an ITC, unless the sponsor accepts the cost-minimised price.

A narrow interpretation of clinical data

For some therapies, the conclusion of value is based on a single clinical outcome measure, e.g. overall survival. This narrow and conservative approach is particularly problematic for the evaluation of rare diseases and diseases with heterogeneous aetiology. The clinical significance of new treatments should also include other endpoints such as secondary clinical outcomes, patient reported outcomes and carer benefits to evaluate the value of innovative medications more holistically and help contextualise uncertainty.

A conservative approach to budget impact modelling

The PBAC recommendations appear increasingly focused on expenditure estimates and managing uncertainty by preferencing highly conservative assumptions, rather than the most likely assumptions,

in estimates of budget impact. Accepted estimates of utilisation and expenditure frequently do not reflect optimal treatment of all eligible patients. As such, expenditure caps have become a duplicative tool that further reduce cost-effectiveness.

Case Study: Comparisons with other similar HTA bodies

In 2020 Phan et al[28] presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Asia Pacific 2020 conference, a *Comparison of Long-Term Overall Survival With Extrapolated Overall Survival for Pembrolizumab Assessed by Australian Reimbursement Authorities*. The authors concluded that 'when compared to the corresponding NICE STAs for melanoma (TA366), sponsor-preferred extrapolation was more conservative than ERG-preferred extrapolation and identical for NSCLC (TA447)[29]. In contrast, the PBAC-accepted extrapolations underestimated OS to a greater extent compared with ERG-preferred extrapolations'. Additionally, that 'Overall, the underestimation of OS and relatively short time horizons preferred by the PBAC suggest that the value of pembrolizumab in these indications may have been underestimated'.

Gordon et al (2021) reviewed international HTA evaluations to identify determinants of value and access for NSCL treatments. The analysis included 163 HTAs that assessed oncological treatments for NSCLC from 2003 to 2019. The authors concluded that 'The effect of the HTA agency responsible for the decision was found to be significant, with HTAs assessed by PBAC substantially less likely to result in a positive outcome than those assessed by other agencies'.

[28] Phan K, Dehle F, Spiteri C, Toomeh E, Bohensky M, Taylor C. Comparison of Long-Term Overall Survival With Extrapolated Overall Survival for Pembrolizumab Assessed by Australian Reimbursement Authorities. ISPOR; 2020. Available at: https://www.ispor.org/docs/default-source/asia2020/bohenskyispor-apeposter-pdf.pdf?sfvrsn=1b86576e_0

[29] Bullement A, Meng Y, Cooper M, Lee D, Harding TL, O'Regan C, Aguiar-Ibanez R. A review and validation of overall survival extrapolation in health technology assessments of cancer immunotherapy by the National Institute for Health and Care Excellence: how did the initial best estimate compare to trial data subsequently made available? J Med Econ. 2019 Mar;22(3):205-214. Available from: https://pubmed.ncbi.nlm.nih.gov/30422080/

Comparator selection

Q2 Recommendations – Comparator selection

12. The comparator should be the therapy(ies) **most likely to be replaced in clinical practice** by the new intervention, aligned with other HTA bodies and good HTA practice. This is consistent with the earlier interpretation of the National Health Act (pre-2015).
13. **Where there are multiple comparators,** the economic assessment should calculate a weighted average price for the new therapy based on the proportion of use that it replaces for each of the comparator therapies.
14. Explore ways to overcome issues facing medicines where the **clinically appropriate comparator has been commoditised**.

Defining the comparator(s) is a critical component of any reimbursement submission. The *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee* stipulate 'the main comparator should be the therapy that prescribers would most replace with the proposed medicine'[30]. This is logical given that the analysis seeks to determine the clinical and economic impact of replacing current practice with the proposed intervention. This approach reflects the expected economic impact and so is consistent with HTA best-practice principles and comparable international HTA organisations.

Lowest cost comparator

Since around 2015, the PBAC has frequently applied a lowest cost comparator approach, even when the lowest cost comparator may be a little-used product in F2 that has been superseded in clinical practice by newer therapies, based on its current interpretation of the National Health Act, Section 101(3B). This disincentivises innovation and does not reflect the economic value of introducing the new therapy. Moreover, choosing a comparator that is not a clinical comparator jeopardises the integrity of HTA and indicates perverse use of LCC for cost containment purposes.

The two key issues with applying the lowest cost comparator approach are:

a) that it does not reflect the true value of the new therapy because it does not allow pricing at parity to the most commonly-used alternative, and
b) that it acts as a barrier to accessing innovative treatments, which can compound over time as newer therapies are also directly or indirectly price-referenced to an older, increasingly rarely-used lowest-cost comparator.

[30] Pharmaceutical Benefits Scheme. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee Version 5.0. Australia: PBS; 2016. Available from: https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf

A selection of case studies that highlight the issue is presented in **Table 5**.

Table 5: Comparator case study summary

Product /date of consideration	**Context**	**Implication**
Price referencing to lowest cost comparator		
Beclomethasone with formoterol – March 22	Reference priced to lowest cost comparator ICS/LABA despite superior clinical evidence	Undervaluation of innovative medicine
Diroximel fumarate – March 22	Reference priced to lowest cost comparator dimethyl fumarate / interferon beta despite superior clinical evidence	Undervaluation of innovative medicine
Risankizumab – November 21	Reference priced to lowest cost comparator infliximab despite superior clinical evidence	Undervaluation of innovative medicine
Carmellose and hypromellose – July 19	Reference priced to lowest cost comparator, preservative free eyedrops	Referenced to lowest cost comparator despite likelihood of substitution for higher-priced comparators in clinical practice
Tocilizumab subcutaneous administration form – March 16	Reference priced to lowest cost comparator IV infliximab despite being unlikely to replace this treatment option in clinical practice	Referenced to lowest price comparator despite likelihood of substitution for higher priced comparators in clinical practice
Delay to patient access		
Ustekinumab – July 22	Submission made 2 years after registration due to likelihood of requiring reference pricing to lowest cost comparator	Delay to Australian patients of innovative medicine
Risankizumab new dose form – November 2021	Inability of a new dosage form to list due to reference pricing to lowest cost comparator	Delay to Australian patients of innovative administration form
Guselkumab pre-filled pen (PFP) new dose form – July 2020	Inability of a new dosage form to list due to reference pricing to lowest cost comparator	Delay to Australian patients of innovative medicine

Abbreviations: ICS/LABA: Inhaled corticosteroids + long-acting beta antagonists

The original intent of the PBAC Guidelines was for the comparator to be the *medicine(s) most likely to be replaced in clinical practice.* As demonstrated, the requirement for new medicines to be price referenced to the lowest cost comparator has, in some cases, resulted in novel medicines being delayed or even not launched in Australia. This issue could be overcome by allowing price referencing to the medicines most likely to be replaced as per the Guidelines, or for a weighted price to be applied in cases where there is more than one appropriate comparator with different prices.

Clinically appropriate but low cost comparator

In 2007, PBS items were separated into two formularies, F1 and F2. F1 consists of medicines with only one brand listed, and F2 consists of medicines with a variety of brands (i.e. generic or biosimilar competitors). This allows different pricing rules to apply to each formulary. In particular, it allows price reductions to be applied to F2 products, which have lost exclusivity and are subject to competition, without these lower prices flowing on to prices of products on F1.

However, the benefits of competition in F2 cause real issues for new medicines which must compare themselves to a low-priced F2 comparator, in order to seek reimbursement. The evidence needed to demonstrate cost-effectiveness over such a low-priced comparator becomes a real hurdle to patient access.

Nowhere is this more evident than in relation to antimicrobials. Novel antimicrobials are generally undervalued by traditional reimbursement systems relative to the benefits they bring to society as indispensable, life-saving drugs. This is because of the existence of low-cost comparators which are still effective for many infections, and the focus of HTA only on direct health costs and benefits. The societal benefits of having a readily accessible supply of novel antimicrobials are enormously valuable, and include fighting resistant infections as well as enabling surgeries, cancer treatments and organ transplants.

The pipeline of new antibiotics remains limited. Reasons include low research investments, limited commercial prospects, and scientific challenges.[31] Governments are exploring policy options for providing new market incentives to drug developers. For example, in France, Germany and the US, implemented interventions centre on providing exceptions in cost-containment mechanisms to allow higher prices for certain antimicrobials.[32]

Global head offices of pharmaceutical companies would refrain from introducing a new, innovative medicine in Australia where the value is being compared to generics/biosimilars that have been

[31] Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Netherlands: Health Policy; 2021 Mar; 125(3): 296-306. Available from: https://pubmed.ncbi.nlm.nih.gov/33402265/

[32] Ibid

subject to price competition and price disclosure impact. Coupled with PBAC's conservative interpretation of evidence and application of the reference pricing policy, this is impeding Australian patient access to innovative medicines or formulation improvements that confer incremental and clinically meaningful benefits.

As other Governments have done, there should be consideration as to how to overcome issues facing medicines where the clinically appropriate comparator has been commoditised.

Real World Evidence

Q2 Recommendations – Real World Evidence

15. Adopt a high level, principles-based framework for **accepting and assessing RWE**.
16. Develop **standards for the utilisation of RWE** for post-marketing monitoring in the reimbursement context. This would require enhanced system infrastructure to **centralise linked health data** and provide appropriate access to stakeholders, including industry.

Real world evidence (RWE), or observational data, is fundamentally changing healthcare by providing a more complete picture of the safety and effectiveness of medical technologies in 'real-world' patient populations. RWE provides evidence of the usage and potential benefits or risks of a medical product[33]. Common sources include electronic health records (EHRs), hospital episode data, claims data (PBS and MBS) and patient registry data (product and disease), chart reviews, clinical audits, and observational cohorts. RWE is important both in supporting ethical study design and overcoming design limitations of randomised controlled trials (RCTs). High quality evidence may be generated where there are clear frameworks that detail the data elements, characteristics, and the internal validation processes to be used.

The available evidence on relative effectiveness and risks of new health technologies is often limited at the time of health technology assessment (HTA). This can cause delays in funding due to concerns regarding the precision with which the magnitude of clinical benefit can be estimated. RWE can help provide a more complete picture of the safety and effectiveness of medical technologies in addition to clinical trial data, facilitating earlier access.

RWE can be used to support claims of efficacy or safety in reimbursement applications, regulatory approvals or monitor outcomes in the post-marketing setting, in addition to clinical trial data. It is often used in situations where the data is scarce or where randomised controlled trials (RCTs) are not feasible or ethical (e.g., rare diseases and paediatric populations).

[33] U.S. Food and Drug Administration. Real-World Evidence. USA: United States Government; 2022. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Australia currently lacks clear guidance on how RWE will be considered in regulatory and reimbursement evaluations. Additionally, access and poor linkage of healthcare data sources prevents sponsors (usually pharmaceutical companies) from generating robust Australian RWE that could present better evidence for HTA and enhance decision making. Broader access to system level data and a linked dataset is also required to realise the full potential of RWE in HTA.

Examples where RWE has been accepted include treatment pattern analysis, estimating the size of patient populations and financial impact, and informing real-world comparator data[34]. In other scenarios, the role of RWE is less clear and its acceptance can be inconsistent. There is hence a need for guidance on when and where use of RWE is appropriate, how to demonstrate its relevance, and developing standards for data integrity.

The use of RWE is under active consideration by the TGA.[35] This provides an opportunity to achieve consistency and efficiency between registration and reimbursement. It is noted that because Australia is a small market in the global context, consideration should be given to alignment with global norms.

Table 6 below provides a summary of where RWE has been used for various reasons in the reimbursement process (relative treatment effect, Managed Access Program, re-assessment of RSAs).

Overall, there are inconsistencies in the application of RWE in HTA, with RWE primarily accepted for the purpose of determining clinical efficacy and relative treatment effect in situations where RCTS are hard to conduct (small populations, paediatric populations).

[34] Medicines Australia - Oncology Industry Taskforce. THE EVOLVING ROLE OF REAL-WORLD EVIDENCE IN AUSTRALIA. Australia: Medicines Australia; 2020 Available from: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2020/11/Oncology-Industry-Taskforce_-Real-World-Evidence-in-Australia-Report-NOV-2020.pdf

[35] In May 2021, the TGA commissioned a rapid review including around 50 targeted stakeholder interviews on their understanding, and use, of RWE and patient-reported outcomes (PROs).

Therapeutic Goods Administration. Real world evidence and patient reported outcomes in the regulatory context. Australia: Australian Government; 2021. Available from: https://www.tga.gov.au/sites/default/files/real-world-evidence-and-patient-reported-outcomes-in-the-regulatory-context.pdf

Table 6: RWE use in PBAC submissions

Drug	Blinatumumab (PSD Jul 2019)	Avelumab (PSD Jul 2018)	Sapropterin (PSD Nov 2018)	Crizotinib (PSD Mar 2017, Nov 2013)	Botulinum toxin type A (PSD Mar 2018)
Disease	B-cell precursor acute lymphoblastic leukaemia (B-ALL)	Merkel cell carcinoma (mMCC), 2nd line	hyperphenylalaninaemia (HPA) due to phenylketonuria (PKU) (children/ adolescents)	ALK-positive, advanced NSCLC	Chronic migraine
Population size	Small/rare	Small/rare	<2000 patients	70-80 patients	5400 patients
Trial evidence for intervention	single arm study	single arm, open label studies	single arm, open label studies		Retrospective chart review of patient on PBS treatment
RWE type	Registry dataset - retrospective historical cohort study Propensity score indirect analysis – blinatumomab vs historical control	retrospective observational cohort naïve indirect comparison	Registry datasets – 2 registry analyses	Registry dataset DoHAC – fact of death data	Comparison of response outcomes is achieved by patients on the PBS with the pivotal trials
Purpose	Comparative efficacy (treatment effect)	Comparative efficacy (treatment effect)	Comparative efficacy (treatment effect)	MES/MAP – to confirm the survival outcomes of the phase III clinical trial (first 50 PBS patients over 2 years)	Supporting a revision of the risk sharing arrangement
PBAC outcome	RWE accepted	RWE accepted	RWE accepted	RWE accepted	Not accepted
Time to access (submission to listing)	3 submissions 17 months (listed Dec 2019	1 submission 14 months (listed May 2019	2 submissions 14 months (listed May 2019)	3 submissions 24 months (listed July 2015)	-

The operating model for centralisation of linked health data by Australian government agencies aligns with the current Australian data reforms and is supported by experts involved with the decision-making process in Australia. A critical step to position RWE as more integral to decision-making is strengthening the foundation of well-characterised longitudinal, representative patient-level real-world data including the richness of variables across sources with demonstrated quality and transparent methods for linkage (Pratt 2019).

The effective use of RWE in the reimbursement setting would allow all available evidence to be considered in the decision-making process and potentially lead to faster patient access to treatments.

Learnings can be taken from countries that are further progressed in setting up the infrastructure to collect these data, linking it across the multiple sources (e.g. US, Sentinel System) and developing systems or protocols for assessing RWE (e.g., NICE RWE Framework).

Detailed Recommendations

- Adopt a high level, principles-based framework for accepting and assessing RWE. This would be a single standard that would be used by the Pharmaceutical Benefits Advisory Committee (PBAC), Medical Services Advisory Committee (MSAC) and other Australian decision makers. This could be based on the UK NICE Framework[36].
- Develop standards for the utilisation of RWE for post-marketing monitoring in the reimbursement context. This would require enhanced system infrastructure to centralise linked health data and provide appropriate access to stakeholders, including industry. It would cover provisional listings, managed entry, or other interim funding mechanisms. A proposed model of linked health data would require:
    - Independent entity or entities aligned to other best practice approaches internationally
    - Government investment to implement capability, with a user-pays pricing model
    - Common data model that transforms data into common formats using standardised terminologies and vocabularies
    - Governance structure that is single, independent, scientific and allows for ethical review of projects. This would remove duplication of ethical and scientific review of projects by multiple jurisdictional entities.

The recommendations above would include evolving the existing AIHW datasets[37] to be utilised for approved purposes, including generating evidence for reimbursement submissions and conducting post-marketing studies.

[36] The NICE Strategy 2021-2026 has recognised that RWD is essential to enabling rapid, robust, and responsive technology evaluations and dynamic, living guidelines. NICE has developed an RWE framework which provides in-depth guidance and tools to support the implementation of these core principles across different uses. There is early engagement with NICE Scientific Advice if sponsors plan to use real-world data in their submissions as part of their evidence-generation plans. To make this easier, the UK's regulatory agency (MHRA) has guidelines on using real-world data to support regulatory decisions.

National Institute for Health and Care Excellence. NICE strategy 2021 to 2026. UK: NICE; 2021. Available from: https://static.nice.org.uk/NICE%20strategy%202021%20to%202026%20-%20Dynamic,%20Collaborative,%20Excellent.pdf

[37] Australian Insitute of Health and Welfare. Data linkage [Internet]. Australia: Australian Government; 2021. Available from: https://www.aihw.gov.au/our-services/data-linkage

Transparency in decision-making

Q2 Recommendations – Transparency in decision-making

17. Create a framework for **predictable, consistent and transparent incorporation of contextual factors**, such as patient and consumer input, severity of disease, equity, confidence in the evidence, assumptions and other relevant factors into HTA decision making.

The PBAC needs to determine the acceptable limit of incremental cost for the benefit gained (also known as the ICER). This limit is varied to account for a range of contextual factors. The PBAC submission guidelines list several 'Other less-readily quantifiable factors that also influence PBAC decision making'. These include among others: severity of disease, equity, presence of available therapies, confidence in the evidence and assumptions, public health issues as well as 'Any other relevant factor that may affect the suitability of the medicine for listing on the PBS'. However, the publicly available information does not provide much clarity on the extent to which each of the contextual factors influence committee decisions. This lack of clarity limits the ability to discuss the logic or evidence behind the judgment and assess its alignment with public policy and interests.

An HTA system could be reduced to a series of calculations, which whilst highly predictable and transparent is unlikely to retain the flexibility required to address the nuances of each submission. It is important therefore to retain flexibility whilst at the same time implementing sufficient structure to allow sufficient transparency and predictability. Transparency promotes accountability and provides information for citizens about what their government is doing. In the case of the HTA of medicines, transparency allows the judgments made by HTA bodies to be assessed with regards to alignment with public policy and interests.

MA considers that much of Australia's HTA system is sufficiently transparent and works effectively. The processes are standardised and published, as are submission guidelines. An account of PBAC meeting discussions is provided in PSDs, and the process has clear timelines. However, further transparency and structure is desired regarding the incorporation of these contextual factors that are not part of ICER calculation. For example, vaccines appear to be subject to a relatively low ICER limit compared with, for example, cancer medicines. It is not clear why this is and whether this aligns with public interest.

Keeping the contextual factors separate from the clinical and economic base-case analyses would allow for more consistent and transparent evaluations. For example, if the PBAC has concerns regarding the uncertainty of the magnitude of clinical benefit and/or other factors such as budget

impact, these should be discussed and addressed as separate matters rather than biasing the interpretation of clinical evidence and economic analyses to compensate for these factors.

Potentially, the extent to which each of the contextual factors influenced the decision could be acknowledged through a scoring system. Multi-criteria decision analysis and ICER modifiers are two ways this could be achieved, though may be overly burdensome to implement and too rigid. An approach where each contextual factor that influenced the decision regarding the maximum ICER was listed and scored, on a Likert 5-point scale for example, as to the extent to which the contextual factor influenced the maximum acceptable ICER would serve a middle ground alternative.

It is also important to ensure transparency in how consumer input is utilised in decision making. This should be a consideration for the work that the Government is undertaking in parallel to the HTA Review, to develop a new process to elevate the patient and consumer voice in access to medicines as agreed to in the Strategic Agreement with MA.

It is well recognised that certain information provided by Sponsors in their submissions is commercially sensitive and warrants protection as confidential information. Sponsors are fully transparent in bilateral discussions with the government, but there are different considerations with the broader community.

2.3 Horizon Scanning

Q2 Recommendations – Horizon Scanning

18. Co-develop and implement a **Horizon Scanning Roadmap**, detailing the steps all stakeholders must take to implement nationally coordinated horizon scanning, to deliver on the commitment of clause 6.2 in the Strategic Agreement.

Horizon scanning is essential if Australia is to be a global priority for the launch of new and innovative medical treatments. Without nationally coordinated horizon scanning, there is a risk of lengthy delays in introducing transformative therapies that fall outside the scope of the current regulatory and reimbursement assessment systems.

Emerging therapies, such as gene therapies, often possess unique characteristics that require novel evaluation approaches. In addition, these therapies can pose other challenges to the healthcare system, such as the need for complex clinical delivery protocols and potential strain on health budgets due to their high-value nature as one-time treatments.

By conducting horizon scanning, governments, patient groups, and industry can anticipate the arrival of these transformative treatments and adequately prepare for their assessment, including establishing appropriate regulatory frameworks and evaluation methodologies. In recent years there have been increasing calls for nationally coordinated horizon scanning to better prepare Australia for the arrival of new and innovative health technologies, thereby facilitating faster patient access.

In recognition of this need, the *Strategic Agreement* commits to the "shared ambition to promote greater understanding and insight into the new medicines, vaccines, and new and emerging technologies coming through development pipelines, in order to facilitate faster access for Australian patients" (paragraph 6.2.1). Furthermore, the Agreement states that Medicines Australia will host, and the Commonwealth will participate in, an annual forum of participants in the innovator medicines sector to:

- identify major therapeutic advances which may enter the regulatory or reimbursement systems (or both) over the following 18-24 months and which may represent a significant disruption in the treatment paradigm and/or require innovation in health care system planning; and
- understand the potential implications for the Commonwealth from the introduction of these advances in terms of resources, systems and processes (paragraph 6.2.2).

In December 2022, Medicines Australia hosted the first Horizon Scanning Forum: Medicines of Tomorrow in Canberra and online. The landmark event brought together stakeholders from across the Commonwealth Government, State and Territory Governments, the medicines industry, life sciences companies, researchers, clinicians, and patient organisations. The Forum explored how horizon scanning could enable the sector to forecast Australia's future health needs better and facilitate faster access to new and emerging medicines for Australian patients.

We have a unique opportunity to harness the momentum generated by the Forum and embrace the spirit of collaboration that the event inspired. The Forum demonstrated the value and importance of nationally coordinated horizon scanning in Australia, with shared support from the presenters, panel members and attendees. Cutting-edge science holds immense promise, but that promise will not be realised unless we have the right policies, processes, and systems to ensure rapid patient access to transformative therapies.

As outlined in Medicines Australia's summary report of the event[38], three key themes emerged:

1. The undeniable need for horizon scanning now

[38] Medicines Australia. Medicines of Tomorrow: Australia's First Horizon Scanning Forum. Australia: Medicines Australia; 2023. Available from: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2023/06/MA-Horizon-Scanning-Forum-v5-June-2023.pdf

The COVID-19 pandemic has highlighted the necessity of disruptive innovation in order to effectively prepare for similar crises in the future. There is a strong and urgent need for nationally coordinated horizon scanning in Australia to ensure patients can access innovative, transformative treatments as quickly and safely as possible.

2. Meaningful co-design of fit-for-purpose horizon scanning

Medicines of Tomorrow was a powerful conversation starter. The time is now to harness the opportunity by working collaboratively to define the purpose of horizon scanning and create a practical framework to ensure immediate and ongoing success.

3. Preparedness and planning are critical to the delivery of the medicines of tomorrow

Scanning the horizon to collect data is not enough. For horizon scanning to be meaningful and effective, there needs to be a commitment to act on the data to prepare our healthcare systems.

2.4 Multi-Sponsor combination treatments

Q2 Recommendations – Multi-Sponsor combination treatments

19. Seek **guidance from the ACCC on competition law** to enable discussion between multiple Sponsors at time of submission and PBS listing.

The use of combination treatments has been increasing over time with greater scientific understanding of the complex pathophysiology of disease. As combination treatments target multiple pathways and levels of a disease simultaneously, they exhibit greater clinical efficacy than single-agent treatments.

Despite the clinical value that combinations provide, there are barriers to access that relate specifically to combinations when the components are marketed by different companies. This is compounded where a new therapy is added to the existing standard of care, where patients may remain on treatment for longer because of the improved health benefits by adding the new therapy. This leads to cases where the new therapy is not considered cost-effective even at a very low, to zero, price.

Even when neither therapy is standard of care, the combination will typically require a combination price lower than the combined list prices of the components.

In either of these scenarios, to be considered cost-effective by PBAC at a price acceptable to the Sponsor companies, the value/price needs to be appropriately divided between the manufacturers of each product.

The New Frontier Report identified the need to improve how combination treatments are assessed and funded in Australia. The report notes that the current system was developed before combination treatments were commonplace as is becoming the case today.

The barriers to access are listed below.

Concerns of potential non-compliance with competition law when the components are marketed by different companies

Manufacturers remain extremely cautious about engaging in combination pricing related arrangements due to a lack of clarity regarding how, and when, this can be done compliantly. Additionally, there may still be scenarios where combination pricing arrangements would be perceived as anti-competitive yet be in the public interest.

The HTA and PBS listing processes are not set up for combinations.

There is no published process for scenarios assessing and listing combination therapies marketed by different companies. Therefore, it is not clear to sponsors how to engage with listing a combination in this scenario.

In certain cases sponsors of the partner product may be inadequately incentivised to engage in combination pricing arrangements causing considerable delay to patient access for the combination

There are scenarios where the sponsor of the partner product may be disincentivised to participate in a combination pricing arrangement. The only viable solution for the Sponsor of the new therapy would typically then be to wait until the price of the partner product has sufficiently eroded, which may not be until one or more years after the partner product's patent has expired.

Medicines Australia recommends that guidance be sought from the ACCC on competition law to enable discussion between multiple Sponsors at time of submission and PBS listing.

Such guidance could clarify under which scenarios and conditions, manufacturers may compliantly conduct inter-company discussions relating to the pricing of components of combination therapies. It could:

- Be co-developed by the Department, Industry and the ACCC.
- Be sufficiently specific to remove legality concern as a barrier to access for the scenarios where inter-company combination pricing discussions are permitted.
- Detail the scope of the discussions permitted, together with the measures/safeguards required to remain compliant under each of the scenarios presented.
- Specify the circumstances where interaction with the ACCC would be required, together with the nature of the interaction and process.
- Give consideration to the legality of different types of commercial arrangements designed to increase the attractiveness of launching the combination at the earliest possible time.
- Implement any necessary changes to the PBAC and Post-PBAC processes to efficiently accommodate multi-sponsor combination submissions.

2.5 Interaction with Evaluators

Currently there is no opportunity for Evaluators to ask clarifying questions or request further information from Sponsors prior to finalising their evaluation report. Resolving as many issues as possible during the evaluation process, prior to the commentary being finalised, would potentially reduce the number of issues for the sub-committees and the PBAC to resolve and reduce the chance of a resubmission.

Clause 6.8 of the *Strategic Agreement* outlines a workstream around the exchange and sharing of information which is running in parallel to the HTA Review, which should go some way towards addressing these concerns. Opportunities include providing points of clarification and any additional data that may assist in the evaluation. Medicines Australia has developed a separate discussion paper on this topic and is currently in discussions with DoHAC around establishing a pilot.

Q3 – Barriers to equitable access

Inequity manifests in a variety of ways including clinical (rarity of disease and variability across disease states) and geographic (variability between states and across metropolitan, rural and regional areas). Economic inequity is also an issue. Most cancer patients, for example feel the economic impact of treatment, with many now bearing a higher proportion of costs for the medicines they need through the private market and crowdfunding[39].

Cell and gene therapies, and therapies for rare diseases, are both presented in this chapter as prime illustrations of inequities arising from the current system. Genetic and genomic technologies are also discussed in this context.

Cell and Gene Therapies

Q3 Recommendations – Cell and gene therapies

20. Establish a **single HTA assessment body** for cell and gene therapies to remove current inconsistencies and complexities to streamline the pathway for patient access:
    - This could be one of the existing bodies, such as the PBAC or the MSAC, an entirely new body, or an expert advisory committee under one of the existing bodies.
    - It is important that any HTA criteria are consistent across all medical technologies, with some consideration for the unique HTA aspects of cell and gene therapies (such as high-value, one-off treatment).
21. Establish a **single federal funding source** for the product costs of cell and gene therapies, similar to PBS funding of medicines.
22. Streamline and, where appropriate, **standardise the clinical delivery of cell and gene therapies** to ensure equitable patient access and improved quality of life for patients and autonomy for clinicians to best meet the needs of patients under their care.
    - The Federal and State Governments and private health insurers must give serious consideration to how equitable access can be given to patients regardless of the public/private clinical setting or location.

There are other recommendations throughout this submission for improvements to the current processes and ideas for system reform, that are also relevant to cell and gene therapies.

[39] Rare Cancers Australia. Counting the cost: the true value of investing in cancer treatment; 2022. Available from https://bit.ly/3KPRe3I

Globally, there are currently over 1200 clinical trials for cell and gene therapies. Around 140 of these are in late-stage development[40]. In Australia, only four cell and gene therapies are currently publicly funded.[41] The HTA and funding pathways for these therapies have been cumbersome and inconsistent, leading to slow and inequitable patient access (see **Table 7**). Given the large number of cell and gene therapies that are set to be launched in Australia in the coming years, it is vital that Australia addresses the barriers that stop the earliest possible, and equitable, access for Australian patients to these therapies.

Table 7: *Publicly reimbursed cell and gene therapies in Australia and their time from registration to Federal funding*

Branded Technology	Indication	Technology Type	TGA Approval[42]	TGA Classification	HTA Body	Funding Program	Setting	TGA registration to Federal funding[43] (days)
Kymriah (Novartis)	Treatment of acute lymphoblastic leukemia in <=25 years old	Cell Therapy	19-Dec-18	Class IV Biologic	MSAC	NHRA	In-patient	117
Kymriah (Novartis)	Relapsed or refractory CD19-positive DLBCL, PMBCL and TFL	Cell Therapy	19-Dec-18	Class IV Biologic	MSAC	NHRA	In-patient	405
Yescarta (Gilead)	Relapsed or refractory CD19-positive DLBCL, PMBCL and TFL	Cell Therapy	11-Feb-20	Class IV Biologic	MSAC	NHRA	In-patient	551
Luxturna (Novartis)	Treatment of biallelic RPE-65-mediated Inherited Retinal Dystrophies	Gene Therapy	5-Aug-20	Medicine	MSAC	NHRA	In-patient	573
Zolgensma (Novartis)	Spinal muscular atrophy (babies)	Gene Therapy	01-Mar-21	Medicine	PBAC	PBS	Outpatient	426

Cell and gene therapies differ from traditional medicines because they often target the underlying cause of the disease. As such, cell and gene therapies have the potential to cure disease and deliver

[40] GlobalData. Australia's Regenerative Medicine Global Pipeline Tracker. Australia: AusBiotech; 2022. Available from: https://www.ausbiotech.org/documents/item/673

[41] See **Table 7**.

[42] TGA approval dates are sourced from the TGA's ARTG Database. Available from: https://www.tga.gov.au/resources/artg

[43] For NHRA funded therapies, 'Federal funding' means the date where the Federal Government publicly announced that funding via States and Territories were available. Note that each State and Territory may have a different start date for funding, as described further down in this section.
For the PBS funded therapy, 'Federal funding' means the funding date as per the PBS Medicines Status Website: https://www.pbs.gov.au/medicinestatus/home.html

long-term benefits. They cannot readily be compared to palliative options or long-term chronic treatments.

Cell and gene therapies can either remove or stop harmful genes or introduce a healthy functioning gene. Oftentimes, these therapies address a high unmet clinical need as they target severe and degenerative genetic conditions where there are no other available treatment options. Timely and equitable access to these life-changing treatments is of utmost importance to patients, their families and caregivers, and clinicians.

The challenges to access can lead to lengthy processes which can be devastating to patients, especially when there are narrow time windows to receive the treatment. This is compounded by the potential of some patients falling out of eligibility for treatment as their condition degenerates. The following sections describe the main barriers to access which are specific to cell and gene therapies.

TGA classifications and pathways

The TGA classifies gene therapies as prescription medicines, which are managed by the Prescription Medicines Authorisation Branch (PMAB). Cell therapies are classified as Class IV biologicals, which are managed by the Biological Sciences Section (BSS), Scientific Evaluation Branch (SEB) of the TGA. This includes therapies where the gene is delivered to cells outside of the body, which are then transferred back into the body (for example, CAR-T cells)[44].

The TGA's classification of cell therapies as 'biologicals' is unique among comparable overseas regulators (CORs). This causes confusion and creates regulatory burden for multinational companies. Definitions and classifications need to have global consistency and a global approach. In the UK and Europe, both cell and gene therapies are classified as 'Advanced Therapeutic Medicinal Products' (ATMPs), and industry has consistently been calling on the TGA to adopt this terminology. The barriers caused by the TGA's unique terminology was also a consistent theme in MTP Connect's stakeholder review of the regulatory framework for gene, cell and tissue therapies in Australia[45].

Priority determination eligibility criteria for biologicals, as well as gene therapies regulated as prescription medicines, are inadequate and create obstacles to accessibility when a similar therapeutic product is already included on the ARTG for the same proposed use(s). This is because priority eligibility criteria require sponsors to show "substantial evidence" that a cell or gene therapy provides a "...significant improvement in the efficacy or safety of the treatment, prevention or

[44] https://www.tga.gov.au/sites/default/files/2022-08/report-cell-gene-and-tissue-regulatory-framework-australia-stakeholder-perspectives-tga-response.pdf

[45] MTPConnect. Cell, Gene and Tissue Regulatory Framework in Australia: Stakeholder Perspectives. Australia: Australia: TGA; 2022. Available from: https://www.tga.gov.au/sites/default/files/2022-08/report-cell-gene-and-tissue-regulatory-framework-australia-stakeholder-perspectives-tga-response.pdf

diagnosis...” compared to a therapeutic good that is already included on the ARTG for the same proposed use(s).

In addition, the biologicals pathway is less well defined and significantly more difficult and complex to navigate relative to the prescription medicines pathway. Applications to register Class IV biological products follow a less certain pathway than conventional prescription medicines. The process for biologicals is essentially the same as the former prescription medicines process prior to key TGA reforms in 2015 to 2016, which led to the introduction of the streamlined submission route. Hence, even if a biological is granted a priority designation, the lack of accountability and transparency in the subsequent registration process makes the speed at which Australian patients can gain access to potentially life-saving treatments much less certain and predictable. Finding the right balance between formally adopting an agile regulatory framework that can respond to rapid advances in cell and gene therapies, and committing to target milestones and timeframes, would provide industry with more business certainty.

Furthermore, there is intrinsic disparity between evidence used to support applications for cell and gene therapies compared with an existing standard of care. Pivotal trials used to register cell and gene therapies are conducted in very small patient groups and based on surrogate endpoints. Moreover, cell and gene therapies are one-off treatments requiring long-term follow-up monitoring of patients and the regulatory requirements can vary across countries. This would contrast with an existing “standard of care” whose entry onto the ARTG would have invariably been based on more comprehensive data and established regulatory guidelines which are closely aligned worldwide.

Multiple and ambiguous HTA pathways

The HTA pathways for cell and gene therapies are complex and dependent on whether the therapy is administered in an inpatient or outpatient setting. This creates uncertainty for Sponsors and leads to potential delays to access for patients.

Gene therapies can currently follow two different HTA pathways: PBAC or MSAC. To determine the pathway for a specific gene therapy, sponsors wishing to list a gene therapy on a publicly funded reimbursement program lodge an MSAC application. A Committee comprising of the MSAC Chair, the PBAC Chair and an appointed State/Territory nominee then decides which pathway the therapy should follow.[46] Generally, gene therapies to be administered to inpatients are reviewed by the MSAC and gene therapies to be administered to outpatients are reviewed by the PBAC, except haemophilia gene

[46] Federal Financial Relations. Addendum to National Health Reform Agreement (NHRA), Appendix B: GOVERNANCE PROCESS FOR HIGHLY SPECIALISED THERAPIES. Australia: Australian Government; 2022. Available from: https://federalfinancialrelations.gov.au/sites/federalfinancialrelations.gov.au/files/2021-07/NHRA_2020-25_Addendum_consolidated.pdf

therapies to be administered to outpatients which are reviewed by the MSAC. Cell therapies are currently delivered in an inpatient setting and evaluated by the MSAC.

The PBAC and the MSAC's guidelines, processes and timelines are different, and the assessment criteria may also differ. In addition, the PBAC and the MSAC have different accountabilities to the Government. As the case study below demonstrates, one gene therapy underwent multiple transfers between the PBAC and the MSAC, which caused significant uncertainty and high workload. The existence of these multiple HTA pathways creates undue complexity, which is exacerbated by the lack of clarity of which pathway a specific therapy should follow. To ensure faster patient access, a clear HTA pathway is necessary.

Case Study: Zolgensma – gene therapy for spinal muscular atrophy

Spinal muscular atrophy (SMA) is a rare genetic disease that affects the nervous system. Zolgensma (onasemnogene abeparvovec) is a gene therapy used to treat SMA. Zolgensma was approved by the FDA in 2019, the EMA in 2020 and the TGA in 2021. The therapy became available on the PBS in 2022.

For patients to receive the therapy, it needs to be delivered in a certified centre. By February 2023 there were only two certified sites in Australia, located in NSW and Victoria, that could deliver the therapy. Since then, one site has been certified in Queensland and another one in Western Australia. The certification process for both sites took upwards of 9 months to complete.

Patients with SMA who lived outside the two original certified sites in NSW and Victoria had to travel to these centres to access treatment. To ensure equitable access, the travel costs and accommodation for up to 20 days were funded by the Sponsor.

In the months leading up to the Zolgensma PBAC submission in 2020, there were multiple conversations between the sSponsor and the Department of Health and Aged Care regarding whether the submission should be evaluated by the PBAC or the MSAC. It was decided that the submission would be evaluated by the PBAC, and the sponsor made plans for a July 2020 PBAC submission. However, in May, the sponsor was advised the decision had changed and the MSAC was going to evaluate the submission instead. This raised significant issues for the Sponsor, as the MSAC submission was due one month earlier than what had been planned and the submission had already been formatted in accordance with the PBAC submission guidelines.

After further discussions with the Department, an agreement was made for the submission to remain in PBAC style. The MSAC also allowed a staggered submission process where the submission could be submitted in two parts due to the truncated timelines.

In August 2020, it was advised that under Appendix B of the NHRA, it had been decided that the PBAC would review the submission. Once again, this change caused significant issues for the Sponsor.

- The timing of the Delegate's Overview, which was required for the PBAC but not stipulated for the MSAC, had not been considered by the Committee. Negotiations with the TGA for the Delegate's Overview were required.
- The need for nusinersen to be a comparator rather than natural history data due to the PBAC requirement for a PBS-listed comparator.
- The inability to use the HPP because the submission was not initiated through this process.

Lack of a clear pathway to reimbursement therefore resulted in significant delays to access for Australian patients and took considerable time and resources for the Sponsor, the Department and the reimbursement committees.

High-value, one-off treatments

There are significant challenges associated with gene therapies due to their unique characteristics and high costs. Unlike traditional treatments, gene therapies are intended to be one-time therapies with lifelong benefits, making it difficult to fully assess their long-term value. The high cost of these therapies poses challenges for both payers and the industry, as they deviate from traditional funding models designed for recurring treatments. The budget implications for payers are substantial and further compounded by uncertainties surrounding patient numbers and the exact budget impact. This one-time high-cost model challenges existing reimbursement systems that are structured around incremental value over time. To address these challenges, appropriate payment models in consultation with the Sponsor may be necessary to manage the unique financial aspects of one-time high-cost gene therapies.

In addition, genetic testing confirmation is required for genetic therapy, and in some cases, genetic counselling is also necessary to understand the implications of the detected mutation. However, the lack of genetic counsellors in Australia results in delays in the treatment pathway for eligible patients, potentially hindering their access to timely and appropriate care.

Few delivery centres lead to inequitable patient access

Many cell and gene therapies have complex delivery protocols. For example, the manufacturing process of CAR-T therapy is individualised for the patient using their blood cells, which creates complicated logistics and supply chain networks. This also means that only a few centres can administer the treatments. Each State takes a different approach to certifying these centres and it can take up to a year for a centre to become certified.

There are only six centres across Australia that are certified to administer cell therapies to patients, and only five centres that are certified to administer gene therapies. These centres are based in metropolitan areas, meaning that patients living remotely or in other states must travel to the centres to receive treatment. However, a single trip to the centre is not sufficient as both cell and gene therapies have a clinical requirement to closely monitor patients for a period of at least four weeks after the treatment. This means that patients that do not live within a few hours of the centre must temporarily relocate. Additionally, for gene therapies when there are two or more children in a family with the same diagnosis, the family may need to temporarily separate children undergoing treatment from those who may be eligible in the future, to avoid exposure to the gene therapy vector. These travel and relocation costs for out-of-state and remotely located patients are extremely challenging and currently funded by Sponsors or via arrangements with not-for-profit organisations.

In a country as geographically dispersed as Australia, the limited number of certified centres for administering cell and gene therapies presents a significant barrier to access for patients. The need for patients and their families to travel long distances and temporarily relocate for treatment adds additional burdens and financial strains. Given the complex delivery protocols and the necessity for close post-treatment monitoring, it is crucial to address this inequity of access. Efforts should be made to expand the certification of centres in various locations across the country, ensuring equitable access to these transformative therapies for all patients, regardless of their geographic location.

The NHRA funds cell and gene therapies that are administered in an inpatient setting. At the very core of the NHRA are principles to ensure equitable access to public hospital services for all eligible persons that are free of charge as public patients, based on their clinical need and regardless of their geographic location. They also give patients freedom to choose whether they are treated as a public or private patient, in a public hospital.

Since the NHRA Addendum 2020–2025 was signed, four highly specialised therapies (HSTs)[47], one of which is a monoclonal antibody, have been recommended by the MSAC and funded through the NHRA: Kymriah – for the treatment of acute lymphoblastic leukaemia in children and young adults; Kymriah or Yescarta (DLBCL) – for the treatment of diffuse large B-cell lymphoma, primary mediastinal

[47] The NHRA Addendum 2020-2025 defines highly specialised therapies as:
HST means TGA approved medicines and biologicals delivered in public hospitals where the therapy and its conditions of use are recommended by MSAC or PBAC; and the average annual treatment cost at the commencement of funding exceeds $200,000 per patient (including ancillary services) as determined by the MSAC or PBAC with input from the IHPA; and where the therapy is not otherwise funded through a Commonwealth program or the costs of the therapy would be appropriately funded through a component of an existing pricing classification.

Federal Financial Relations. Addendum to National Health Reform Agreement (NHRA). Australia: Australian Government; 2022. Available from: https://federalfinancialrelations.gov.au/sites/federalfinancialrelations.gov.au/files/2021-07/NHRA_2020-25_Addendum_consolidated.pdf

large B-Cell lymphoma and transformed follicular lymphoma; Qarziba – for the treatment of high-risk neuroblastoma; and Luxturna – for the treatment of inherited retinal disease (**Table 8**). Access for patients to these HSTs is highly restricted and largely inequitable for eligible patients. This is in direct opposition to the NHRA principles stated above. In addition to the geographic limitations, there is no access for treatment in private hospitals.

Table 8: HSTs funded under the NHRA and their availability

Technology	Company	Therapeutic Indication	Public hospitals in Australia where therapy is administered
Kymriah (tisagenlecleucel) CAR-T therapy (in patient administration)	Novartis	Paediatric acute lymphocytic leukaemia (pALL), relapsed or recurrent adult diffuse large B-cell lymphoma (r/r DLBCL)	6 centres: Peter MacCallum (Vic), The Alfred (Vic), RPA (NSW), Westmead (NSW), Royal Brisbane (Qld), Fiona Stanley (WA)
Yescarta (axicabtagene ciloleucel) CAR-T therapy (in patient administration)	Gilead	Relapsed or recurrent adult diffuse large B-cell lymphoma (r/r DLBCL), PMBCL, TFL	6 centres: Peter MacCallum (Vic), The Alfred (Vic), RPA (NSW), Westmead (NSW), Royal Brisbane (Qld), Fiona Stanley (WA)
Luxturna (voretigene neparvovec-rzyl) Gene therapy (in patient administration)	Novartis	Interrelated retinal dystrophy	2 centres: Royal Victorian Eye and Ear Hospital (Vic), Westmead Children's Hospital (NSW)
Qarziba (dinutuximab beta) Monoclonal antibody (in patient administration)	EUSA Pharma	High-risk neuroblastoma	Royal Children's Hospital (Vic)

Multiple and cumbersome funding pathways

The HTA and funding pathways for cell and gene therapies vary depending on the type of therapy and how it is delivered:

- Gene therapies to be administered as outpatients are reviewed by the PBAC and funded under the PBS.
- Gene therapies to be administered as an inpatient are reviewed by MSAC and funded as HSTs under the NHRA.
- Haemophilia gene therapies to be administered as outpatients are reviewed by MSAC and funded by the National Blood Authority (NBA).
- Cell therapies are evaluated by the MSAC and funded as HSTs under the NHRA.

The various pathways and multiple funders mean that it can take a significant amount of time after a positive recommendation by either the PBAC or MSAC before patients access these therapies.
The NHRA supports delivery of new life-saving high-cost therapies and improve the access to treatment for patients with rare conditions who often have few options remaining[48]. High-cost, HSTs are defined as therapies where the average annual treatment cost at the commencement of funding is more than $200,000 per patient (including ancillary services). The term 'rare conditions' is not defined in Section C of the NHRA.

HSTs are delivered at selected public hospitals only and they are jointly funded by the Commonwealth Government and State and Territory Governments, currently on a 50/50 basis as per the addendum to the NHRA that applies until 2025. In other words, the federal decision maker for approving a cell or gene therapy as a highly specialised therapy only funds half the cost of the therapy, while State and Territory Governments must fund the other half of the cost within capped budgets. While the PBS and the MBS have uncapped budget appropriations, State and Territory health budgets do not. This could create delays in patient access while some jurisdictions process the request through the normal budget channels.

For example, some State and Territory Governments interviewed for a recently published report by Evohealth indicated that they received only short notice that a CAR-T cell therapy would be recommended for public funding by the MSAC in 2019.[49]With no funding allocation set aside and jurisdictional budget cycles misaligned to the timing of the MSAC announcement, State and Territory Governments faced pressure to rebalance health expenditure to secure funding to cover 50 per cent of the cost of delivering CAR T-cell therapy to eligible patients.

For gene therapies that are blood related, funding and access may be co-ordinated by the National Blood Authority (NBA). The NBA was established following the signing of the National Blood Agreement by all state and territory ministers in 2002. Products managed and sourced by the NBA are funded in a 63: 37 split between the Commonwealth and States/Territories.

NBA products are primarily managed through an acute care setting (even if for a maintenance phase of treatment) due to the specialised services and administration requirements of the products. Related services are continually repriced via the Independent Hospital Pricing Authority (IHPA).

[48] Australian Government Department of Health and Aged Care. 2020–25 National Health Reform Agreement (NHRA). Australia: Australian Government; 2022 Available from: https://www.health.gov.au/our-work/2020-25-national-health-reform-agreement-nhra
[49] Beardmore, R, Musgrave, S, Birchall, L, Stanley, R and Sharma, Y. CAR T-cell therapy: Is Australia ready, willing and able? Australia: Evohealth; 2023 Available from: https://evohealth.com.au/insights/car-t-cell-therapy-is-australia-ready-willing-and-able/

Of note, the policy responsibility for ensuring that Australians have equitable and timely access to blood supply is managed with input from the Jurisdictional Blood Committee (JBC). The JBC has member representation from the Australian Government and from each State and Territory.

Detailed Recommendations

Cell and gene therapies have the potential to revolutionise healthcare by targeting underlying diseases and providing long-term benefits. However, their access and funding pathways in Australia have been inconsistent and complex, leading to slow and inequitable patient access. To address these issues, MA makes the following recommendations:

1. Establish a **single HTA assessment body** for cell and gene therapies to remove current inconsistencies and complexities to streamline the pathway for patient access.
    - This could be one of the existing bodies, such as the PBAC or the MSAC, an entirely new body, or an expert advisory committee under one of the existing bodies.
    - It is important that any HTA criteria are consistent across all medical technologies, with some consideration for the unique HTA aspects of cell and gene therapies (such as high-value, one-off treatment).
2. Establish a **single federal funding source** for the product costs of cell and gene therapies, similar to how the PBS funding of medicines.
3. Streamline and, where appropriate, **standardise the clinical delivery of cell and gene therapies** to ensure equitable patient access and improved quality of life for patients and autonomy for clinicians to best meet the needs of patients under their care.
    - The Federal and State Governments and private health insurers must give serious consideration to how equitable access can be given to patients regardless of the public/private clinical setting or location.

Rare Diseases

Q3 Recommendations – Rare Diseases

23. **Identify and track HTA applications for orphan drugs** through reimbursement pathways so that rare disease specific issues can be identified and addressed.
24. Coordinate HTA applications for rare disease therapies through a **single entry point within the DoHAC**.
25. Recognise in the HTA guidelines that, for rare diseases, **observational data is the best evidence available** for decision making.
26. There should be a **direct and streamlined path to funding** via the Life Saving Drugs Program (LSDP).

There are other recommendations throughout this submission for improvements to the current processes and ideas for system reform, that are also relevant to rare diseases.

Australians living with a rare disease should have equitable, timely and sustainable access to medicines

Australians currently wait between two to four years longer than comparable countries[50] for access to rare disease medicines. In some cases, Australian patients miss out entirely on rare disease treatments that are available overseas,[51] where countries have introduced processes tailored for the evaluation of rare disease therapies.

The *National Strategic Action Plan for Rare Diseases* (*The Action Plan*) defines a rare disease as one that affects fewer than 5 in 10,000 people, which aligns with many international definitions and with the TGA criteria for orphan drugs.[52] International benchmarks show that orphan drugs, which target rare diseases, take longer to secure access, compared to other therapies in all countries except Germany and Scotland.[53]

[50] Jackson A, Geatches L. The McKell Institute 2021 Progress Update: Funding Rare Disease Therapies in Australia - Ensuring Equitable Access to Healthcare for all Australians. Australia: The McKell Institute; 2021. https://mckellinstitute.org.au/wp-content/uploads/2022/02/McKell-Funding-Rare-Disease-Therapies-in-Aus-2021.pdf

[51] Ibid

[52] Australian Government Department of Health and Aged Care. National Strategic Action Plan for Rare Diseases, Australian Government. Australia: Australian Government; 2020. Available from: https://www.health.gov.au/resources/publications/national-strategic-action-plan-for-rare-diseases

[53] Centre for Innovation in Regulatory Science. CIRS RD Briefing 83 – HTA outcomes in Australia, Canada and Europe 2016-2020. UK: CIRS; 2021. Available from: https://www.cirsci.org/publications/cirs-rd-briefing-83-hta-outcomes-in-australia-canada-and-europe-2016-2020/

Rare diseases definitions differ across agencies and programs, which can lead to inconsistencies across rare disease policies. A more restrictive definition of fewer than 1 in 50,000 people (sometimes called 'ultra-orphan') is applied for eligibility for funding via the LSDP.[54]

Evaluation processes for rare disease treatments should be adapted to ensure that evaluators understand the limitations associated with rarity and evaluate submissions with a 'rare disease' lens. This would include the importance of understanding the burden of disease, the reliance on different levels of evidence to inform decision-making, and the challenges in demonstrating cost-effectiveness. The importance of a broader valuation of the rare disease product than non-rare products should also be outlined.

Additionally, evaluators should be encouraged to seek input from clinical experts who currently actively treat the particular condition. The number of relevant clinical experts may be very small compared to non-rare products, also making it is more likely that they may have participated in company-sponsored clinical trials. Therefore, relaxation of accepted conflict of interest principles is recommended for rare diseases.

Patient engagement is also critical to understanding the full impact of the rare disease and the meaningfulness of the clinical benefits, and therefore consumer hearings should be offered to patient groups for all proposed rare disease products.

The Action Plan recommends to "broaden the description and understanding of the principles underpinning Australian Health Technology Assessment (HTA) processes to acknowledge the challenges associated with assessing health technologies for rare diseases" (2.4.1.1). *The Action Plan* also recommends to "Ensure rare disease expertise exists, or can be accessed, on all reimbursement pathways and HTA advisory bodies" (2.4.2.3).[55]

A single access point or centre of excellence within the DoHAC would have the benefit of overseeing implementation of activities consistent with *The Action Plan* by monitoring and evolving rare disease policies to ensure Australians have equitable and timely access to therapies.

This may also align with a recommendation from *The Action Plan* to "Build rare disease expertise within the Office of HTA (OHTA)" (2.4.2.1). Additionally, *The New Frontier Report*: "The Committee

[54] Centre for Innovation in Regulatory Science. CIRS RD Briefing 83 – HTA outcomes in Australia, Canada and Europe 2016-2020. UK: CIRS; 2021. Available from: https://www.cirsci.org/publications/cirs-rd-briefing-83-hta-outcomes-in-australia-canada-and-europe-2016-2020/

[55] Australian Government Department of Health and Aged Care. National Strategic Action Plan for Rare Diseases, Australian Government. Australia: Australian Government; 2020. Available from: https://www.health.gov.au/resources/publications/national-strategic-action-plan-for-rare-diseases

recommends the Australian Government establish a Centre for Precision Medicine and Rare Diseases within the Department of Health" (recommendation 1).[56]

The evidence barrier

There are significant challenges with the development of evidence for rare disease treatments. Many studies are small and non-comparative in design. This is due to the small size of the patient population for many of these conditions, and the ethical issues of using placebo for severe and chronic conditions.

Many rare diseases are genetic in origin. This leads to heterogeneity in the disease characteristics in addition to a variable disease history (variability in time to diagnosis, rate of progression, use of prior treatments). This makes comparisons across data sets problematic for small patient populations.

In cases where rare diseases are slowly progressive or degenerative, it is difficult to demonstrate long-term outcomes such as survival in a randomised trial as it is not possible to recruit the necessary patient numbers and deliver results in a reasonable timeframe. Overall survival (OS) is not often formally assessed in trials as patients would not be expected to die from the condition while receiving treatment in the time frame of a study.

The recent NICE Methods Review highlighted the need for different evidence standards to be applied to orphan drugs, and the need for greater acceptance of real-world evidence. That is, evidence that is generated through non-randomised studies, single-arm studies, registry data or other methods of evidence generation.

Early engagement with Australian clinicians could help frame the clinical context for the HTA review

Due to their rarity, the context and nature of the disease is often not widely understood, beyond patients living with a rare disease and their clinicians. Unlike more common chronic therapies, rare diseases may not have an evidence-based clinical management algorithm and may have limited data on the natural history of the disease. Rare diseases are typically managed by a small number of specialised health care professionals and beyond this group there may be limited understanding of the rare disease and treatment outcomes.

Better co-ordination of stakeholders prior to HTA evaluation could facilitate early agreement on place in therapy, comparator and patient relevant outcomes. Early engagement could also have the benefit

[56] House of Representatives Standing Committee on Health, Aged Care and Sport. The New Frontier - Delivering better health for all Australians: Inquiry into approval processes for new drugs and novel medical technologies in Australia. Parliament of the Commonwealth of Australia: Australia; 2021. Available from: https://parlinfo.aph.gov.au/parlInfo/download/committees/reportrep/024755/toc_pdf/TheNewFrontier-DeliveringbetterhealthforallAustralians.pdf;fileType=application%2Fpdf

of allowing associated medical services to adapt to new therapies and technologies, align any co-dependent technologies, update screening programs, consider workforce issues and consider any data collection requirements.

The Action Plan recommends to "build on the current processes within the OHTA to ensure all rare disease submissions are flagged as complex and may require additional scoping and engagement to address potential challenges and uncertainties" (2.4.2.1).

A broader consideration of value is important including the magnitude of clinical benefit, rarity, severity, equity, burden of disease, innovation or scientific advance, budget impact, societal benefits and indirect costs. Although broader aspects are considered by HTA decision makers on a case-by-case basis, more transparency on the factors for consideration and the presentation of this information in HTA applications is required.

In addition, Australian clinical expert input is important to frame the HTA decision for rare disease therapies. More structured engagement with clinical experts for rare disease therapies could inform issues such as the applicability of the evidence or eligibility criteria during consideration of value.

Patients are requesting timely access to therapies

There should be no patient gap – Australia's HTA pathways should enable patients living with rare disease to have access to treatments as soon as practicable after TGA registration. A review across international examples showed that there is no one model of funding that addresses the complexity of HTA review. Japan, Germany, the UK and France have developed specific processes to overcome the challenges of patient access to orphan drugs. These include aspects such as supplementary processes, exclusion of cost-effectiveness analysis in HTA, and higher or more flexible thresholds for funding.

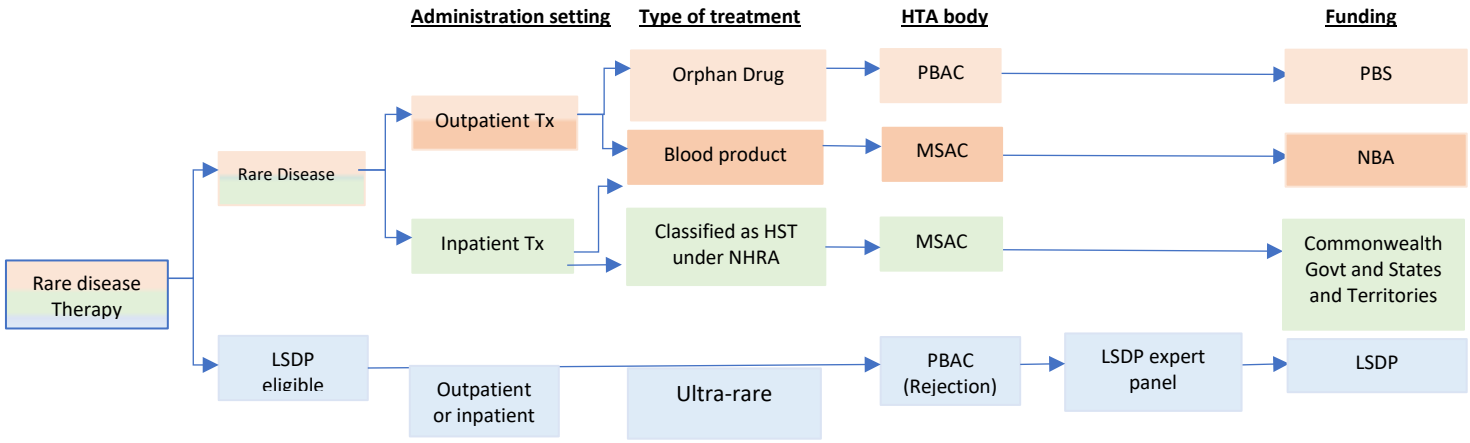
HTA pathways for rare disease have developed over time and need to be streamlined

The HTA pathway can be challenging for sponsors to navigate. Rare disease HTA pathways have evolved over time based on the setting where a patient will access treatment, resulting in multiple inconsistent evaluation pathways as illustrated in **Figure 4** below.

- Rare disease therapies which are administered as outpatients are reviewed by the PBAC and funded on the PBS
- Rare disease therapies that require specialised blood related services are reviewed by MSAC and funded by the NBA

- Rare disease therapies that require specialised hospital related services are reviewed by MSAC and funded by Commonwealth Government and States and Territories under the NHRA
- Some ultra-rare treatments that require specialised hospital related services are reviewed by PBAC, and if rejected for funding on the PBS may be funded by the LSDP if additional criteria are met.

Figure 4: Rare disease treatment HTA and funding pathways



In order to provide a consistent, efficient, and streamlined approach to HTA, the evaluation process should be the same irrespective of the funding or service delivery pathway.

As outlined in **Figure 4**, a 'life-saving' treatment must first be rejected by the PBAC before it can be considered for funding under the LSDP. This adds a minimum 12-month delay to the reimbursement process for rare disease therapies that are eligible for funding on the LSDP.

The New Frontier Report supports a direct and streamlined path to the LSDP: "The Committee recommends that the assessment process for the Life Saving Drugs Program (LSDP) be streamlined and delays in access to treatments be reduced by ensuring that a sponsor only need lodge one application for one Health Technology Assessment pathway" (Recommendation 4).

Genetic and genomic technologies

Challenges in HTA for genetic and genomic technologies are having a negative impact on equitable, affordable, and timely patient access to healthcare across Australia.

Genetics and genomics both play a fundamental role in health and disease. Genetics refers to the study of genes and the way that certain traits or conditions are inherited from one generation to another. Genomics describes the study of all genes within an individual (the genome). Genomics can encompass the scientific study of complex diseases that are typically caused by a combination of genetic and environmental factors as opposed to individual genes (e.g. heart disease, asthma, diabetes and cancer). Genomics offers new possibilities for therapies and treatments for some complex diseases, as well as new diagnostic methods.

Where and how patients access genetic and genomic technologies in the clinical setting is variable, as are the costs incurred by patients. With the predicted increase in clinical use of genetic and genomic technologies in coming years and the speed with which new technologies are being developed and moving from the research to clinical setting, the current access and affordability challenges are likely to grow if left unaddressed. Additionally, the rapid development of genetic and genomic technologies blurs the delineation between research and the clinical setting, challenging existing HTA pathways.[57]

Genetic and genomic technologies are typically evaluated by the MSAC. Genetic and genomic technologies may also be evaluated by other stakeholders, such as state and territory governments or private health insurers.

While MSAC has amended its guidelines for genetic and genomic technologies , the broad industry view is that these amendments are still unclear and insufficient to provide the clarity required. Additionally, the administrative processes associated with applications for genetic and genomic tests will also pose challenges for the current MSAC processes, and more pragmatic solutions may need to be adopted.

Genetic and genomic technologies can be used for several purposes including diagnosis, screening, prognosis, monitoring and for access to targeted therapies. Therefore, the types of genetic and genomic applications considered by MSAC are broad and include:

1. Investigative applications covering diagnosis, screening, prognosis and monitoring
2. Co-dependent applications covering linked genetic/genomic technologies and targeted drugs.

[57] InGeNA. Realising the full potential of genomics to personalise healthcare: Future directions for health technology assessment in Australia. White Paper, March 2022

The MSAC process is challenging for genetic and genomic technologies, as the PICO is complex to define. This is due to the inclusion of multiple patient populations, comparators, and pathways. In addition, cascade testing is often recommended to family members and reproductive partners – which increases the complexity of the application.

The complex funding arrangements for genetic and genomic technologies can also lead to ambiguity resulting in funding delays between states/territories and the Federal Government. This means that technologies can be evaluated at multiple levels including national, state/territory and hospital. Further, there could be delays in evaluating and implementing new technologies if there is a lack of agreement as to who pays.

A report by InGeNA, commissioned in 2022, outlines some of the actions needed to develop a more fit-for-purpose system for genetic and genomic technologies[58].

[58] Ibid

Q4 – Elements that detract from person-centredness

Q4 Recommendations – Elements that detract from person-centredness

27. Formulate a robust and formal framework for **earlier and more meaningful consumer engagement** across the lifecycle of a medicine, to deliver on clause 6.3 of the Strategic Agreement.
28. Provide greater transparency on **the utilisation of consumer evidence and how it informs decisions** made by HTA agencies.

The *Strategic Agreement* has identified the need for policy improvements to ensure patients have improved involvement in the decision-making for medicines access, such as co-creating a new process to elevate patient and consumer voices in access to medicines (Clause 6.3).

Medicines Australia believes in the need for co-creation and any recommendations to strengthen the role of patient engagement must be considered as part of a broader dialogue with patients, led by patients. Our vision is to ensure patients are valued from the commencement of the process and is considered through the lifecycle of medicines.

Consumer engagement in the HTA process

Consumer participation is generally provided late in the decision-making process and consumer participation rate remains low, despite existing platforms for input. Greater consumer engagement that encompasses the lifecycle of medicine and decision-making before, during and after the HTA process will lead to improved outcomes for patients.

Medicines are evaluated on the basis of their clinical benefit and cost-effectiveness, when compared to the standard of care. Outcomes which are of great value to consumers, such as improvements in quality of life and non-health benefits, are often not well measured, and therefore may not be weighted accordingly by decision makers and accurately accounted for in the HTA process.

Consumers have unique experience-based knowledge gained from living with health conditions and using health technologies. Their expertise is currently underutilised when decisions are being made about if, how, and when a new health technology should be adopted in Australia. Providing consumers with the mechanisms to have a greater voice in HTA decision-making process may reduce uncertainties by taking account of the real-life context of consumers.

Greater engagement will increase understanding of HTA and, in turn, increase the capacity of consumers to make valuable contributions. Furthermore, it can lead to a stronger evidence-base for HTA, making the process more robust as it takes account of social values, ethics, and consumer needs, preferences and lived experiences. Overall, greater engagement before, during and after any HTA process may lead to enhanced decision quality at all stages.

It is recommended that the work currently being undertaken to co-design an enhanced consumer engagement process as part of the Strategic Agreement (Clause 6.3) should cover the entire HTA process, including the broader reimbursement lifecycle of a medicine. The framework should enable the breadth and depth of patient evidence to be included as early as possible in the assessment process and explicitly consider and value the broader non-health factors and societal impacts.

Transparency on how consumer evidence is used to inform decisions made by HTA agencies.

The PBAC acknowledges it is committed to understanding consumer perspectives and integrating them into its consideration of medicines and vaccines. However, the current HTA process does not have the ability to provide direct feedback on the outcomes and the value of the consumer evidence in the overall decision-making process.

While consumer input is valued and summarised in individual Public Summary Documents, it lacks specific detail regarding the usefulness and effect of the input on the decision. By doing so it lacks an ability for consumers to understand the value of their contribution and an ability to continuously evolve their level of evidence to support stronger decision-making.

Consumer Hearings are held by the PBAC, when deemed necessary for the therapy being assessed and is often seen as an extension to information submitted via a web-interface. While the hearings provide for direct interactions with the PBAC regarding medical technologies that are being considered for PBS listing, the process lacks transparency.

It is recommended that the PBAC provide transparent feedback, in lay language, to consumers on:

- what was valuable to the Committee;
- what information could have assisted the Committee
- how the consumer input and consumer-based evidence was taken account; and
- how the consumer input weighted on the decision.

Q5 – Perverse incentives

The consultation paper[59] describes perverse incentives "where an element or feature of HTA policy and methods may be creating an unintended incentive that results in negative consequences". Medicines Australia acknowledges that perverse incentives may exist for industry, PBAC, Government and for other stakeholders. Medicines Australia has identified the following issues as potentially creating perverse incentives for industry.

Cost minimisation

It is well known in the Australian HTA system that a cost-minimisation analysis is more likely to be accepted the first attempt compared to a cost-effectiveness analysis. Adopting a cost-minimisation approach may enable a new medicine to be available in Australia, but simultaneously limits the ability to evolve existing decision-making methods, with any outcome modelled on the restriction currently applying to the main comparator. The patient population for the PBS is likely to be narrower than the TGA approval. While there are methods to consider a broadening of the population, the methodology is aligned with uncertainty in PBAC decision-making and greater risk of delaying PBS Listing, with clear impacts on the broader patient population who would benefit from the medicine. Changes to the current methodology are required to ensure the patient population is not limited to previous decision-making or limited to modelling to a current comparator but challenged to ensure there is an appropriately defined population aligned with the totality of available evidence.

Life Savings Drugs Program (LSDP)

The LSDP pays for specific essential medicines to treat patients with rare and life-threatening diseases. Mandatory rejection by the PBAC before being designated a life-saving (or life-changing) drug is counter-intuitive to the 'life-saving' status of these medicines and delays access for people who stand to benefit with potentially devastating consequences.

New Presentations for medicines listed in the F1 formulary

The 2007 legislative reforms introduced statutory price reductions (in sections 99ACB and 99ACD of the National Health Act 1953) to apply when the first bioequivalent or biosimilar brand is listed on the PBS. New presentations for PBS medicines in the F1 Formulary, regardless of how long the medicine has been PBS listed, also trigger a first new brand statutory price reduction. The new presentation

[59] Australian Government Department of Health and Aged Care. HTA Policy and Methods Review, Consultation 1 Survey questions, April 2023. Australia: Australian Government; 2023. Available from: https://www.health.gov.au/our-work/health-technology-assessment-policy-and-methods-review

may deliver better health outcomes and/or quality of life for patients, but the statutory price reduction creates a disincentive for a sponsor to bring the new presentation to market.

Q6 – International Comparisons – Learnings and Observations

From analyses of international systems, the following have been identified as key considerations for Australia in achieving the goal of reduced time between product registration and reimbursed access, with alignment of access criteria to the indication on the regulatory label, while retaining flexibility for Sponsor-led submissions, including the ability for the Sponsor to define the reimbursed population:

- Early engagement to work through important issues in evaluating the clinical and/or economic evidence
- Accelerating access, for example via a provisional access pathway for products meeting certain eligibility criteria (integrated with the standard HTA system, focusing on areas of high unmet need, with re-review within a specified period) or immediate access for new, registered health technologies while HTA is conducted
- Separation of pricing and budget impact decision makers from HTA.
- Legislated timeframes or KPIs for access.

No country has a "perfect" HTA system.

Medicines Australia conducted a comprehensive mapping of end-to-end HTA processes for 7 OECD markets (France, England, Germany, Canada, Austria, Switzerland, and Japan), and commissioned BioIntelect to develop case studies of policies and processes in international HTA systems to identify "best practice", and drivers of success in other countries. The following key elements were considered:

1. Horizon scanning and early engagement
2. Regulatory authorisation/approval facilitating access
3. HTA priority pathways/fast track assessment
4. HTA/value assessment
5. Pricing
6. Contracting
7. Funding.

Key themes started to emerge that appeared to be likely predictors for fast access. These were analysed in a 'heat-map' matrix across the markets and compared to the Australian HTA context to identify potential opportunities for system reform (**Table 9**).

Table 9: Predictors of rapid access to new treatments internationally

	Japan	Germany	Austria	England	Switzerland	France	Canada	Austr
Horizon scanning / joint Scientific Advice								
Early engagement, implementation planning	No	Yes	?	Yes	?	Yes	Yes	No
Pre-alignment on HTA parameters (eg comparator)	No	Yes	?	Yes	?	Yes	Yes	Partial
Regulatory approval								
Parallel registration and reimbursement pathways	No	NA	NA	Yes	Partially	Yes, at least	Yes	Yes
HTA priority pathway / fast track								
Rapid access for special circumstances	Yes	NA	NA	Yes	Theoretica	?	Yes	Partial
Standard HTA / value assessment								
Access available prior to full assessment	Yes	Yes	Yes	Yes	No	Yes, at least	Yes	No
Provisional reimbursement (for eg PhII data)	No	?	?	Yes	?	Yes	Potentially o	Partial (M
Consultation on choice of comparator	No	Yes	?	Yes	?	?	Yes	
Appropriate recognition of incremental innovation	Yes	?	?	Yes	?	Yes	Yes	No
Tolerance for uncertainty & managing risk	No	?	?	Yes	?	Yes, with pr	No	No
Broader value assessment beyond ICER	No	Yes	No	Yes	?	?	Yes	No
Patient perspective incorporated in value assessment	No	Yes		Yes	?	Yes	Yes	Partial
Pricing								
Separation of pricing decision maker from HTA	No	Partial	Yes	Yes	NA	Yes	Yes	No
Initial free pricing period	No	Yes	Yes	No	No	Yes, at least	No	No
Statutory pricing adjustments to on patent medicines	Yes	Yes	Yes	Yes	Yes - redu	?	Yes	Yes
Potential increases to maintenance price	No	?	?	No	No	?	No	No
Contracting								
Separation of contracting decision maker from HTA	No	Yes	Yes	Yes	NA	Yes	Yes	No
Risk sharing beyond price-volume agreements	contracts	No	No	Yes	NA	?	Yes	Partial (M
Funding structures								
Overall funding & budget considerations/sustainability								
Centralised funding via national formulary	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Private health insurance	Yes	Yes (10%)	No (SHI)	Yes (10-20%	Yes	Yes	Yes	No
Other								
Applicant led submissions (not mandated)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Clear timeframes or KPIs for access	Yes	Yes	Yes	Yes	Theoretica	Yes	Yes	No
Gov policy settings prioritising medicine access	Yes	No	?	Yes	?	Yes	Yes	No
Early & continuous stakeholder involvement	Clinicians	Yes	?	Yes	?	?	Yes	Partial
**Time to access: source Medicines Matters*	101	121	155	167	178	322		391

A detailed analysis of international systems can be found in the Appendix.

Q7 – Reforms for consideration

Medicines Australia would like the HTA Reference Committee to consider policy reforms to address the patient access gap. These ideas would require either structural change, changes in the submission process or timelines, rules of engagement and potentially legislative change. How they are used will require flexibility in approach, given that different medicines will have different levels of complexity.

They are not alternatives to each other, but represent a menu of options, of which some or all could be implemented together. The reform ideas revolve around three key areas:

A. Commit to delivering faster access for patients through policy and process reform
B. Reform the HTA system to better enable first time success through the PBAC process
C. In addition to the above, ensure Australia is a first launch country.

A. Commit to delivering faster access for patients through policy and process reform

Q7 Recommendations – Faster access

A. Commit to delivering faster access for patients through policy and process reform, by:
    29. Ensuring all assessment and recommendation processes are aligned to allow for **reimbursement from TGA registration**.
    30. Introducing **interim funding** for certain medicines.

Ensuring all assessment and recommendation processes are aligned to allow for reimbursement from TGA registration

The regulatory and HTA processes in Australia operate in a sequential manner; even the current 'parallel process' does not allow for simultaneous commencement of filings due to dependency on availability of TGA's Delegate's Overview. This slows down the PBAC recommendation.

Patients would be able to access subsidised medicines some months earlier than is possible in today's system through earlier initiation of the HTA process to align with the TGA application. This could involve, for example, removing the requirement for the TGA's Delegate's overview when the PBAC submission is considered.

It would result in medicines being available as soon as practicable after the TGA registration.

Issues related to this concept which require further consideration and discussion

- Misalignment between the TGA registration label and PBAC recommendation
- Could this concept facilitate joint TGA/PBAC evaluation?

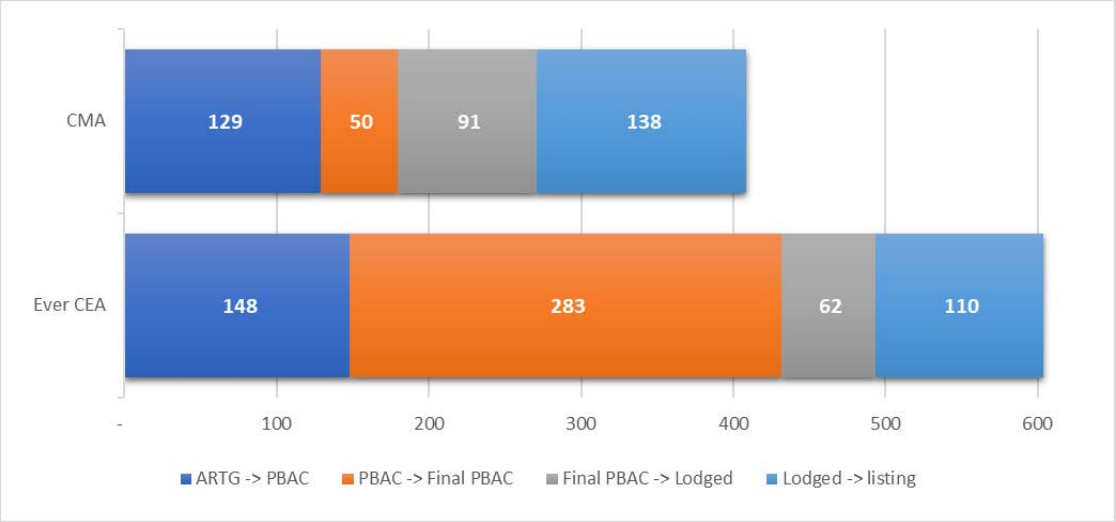
Introduce interim funding for certain medicines

The current Australian system provides reimbursed access to patients only after a full HTA is complete and a final price has been negotiated. In theory, reimbursed access can be achieved within approximately 60 days of TGA registration if: there is parallel processing, a first-time PBAC recommendation, and no unnecessary delays to post-PBAC negotiations. In practice however, there are very few medicines that achieve this.

An analysis of PBAC recommendations, between March 2021 and March 2023, leading to listing (as of 31 May 2023), indicated that 'ever' cost-effective submissions (where cost-effectiveness was utilised in at least one of the submissions leading to the listing) had an average patient access gap of approximately 603 days, with the time between final PBAC decision and PBS listing for these listings being around 172 days.

This represents a delay of almost 6 months, an amount of time which is meaningful to patients.

Figure 5: Patient* access gap (days) March 2021 to March 2023



**PBAC recommendations leading to listing as of 31 May 2023*

Interim funding would enable patients to access subsidised medicines as soon as practicable after a positive PBAC recommendation, while Sponsors and Government finalise negotiations. It could be aimed at those new technologies or expanded indications that provide a substantial improvement in health outcomes compared to relevant alternative therapies.

It differs from the current Managed Access Program (MAP), which requires the Sponsor to go back to the PBAC sometime after the Sponsor's first submission.

The time involved in the provision of interim funding would depend on the pricing pathway used by the Sponsor and the outcome of negotiations between the Sponsor and the Government.

How could this be implemented?

A Sponsor would lodge a submission with applications able to be submitted as early as the point of TGA submission. This removes the current requirement for the PBAC to wait for the TGA Delegate's Overview.

The PBAC submission would include a full HTA assessment, including cost-effectiveness analysis and current processes for evaluation of applications prior to PBAC consideration could continue, including any additional improvements to the process and HTA technical considerations (which are outlined earlier in this submission in Chapter 2).

A positive PBAC outcome would mean that the submission progresses to the next phase of the PBS listing process – price setting and administrative listing processes.

Medicines eligible for interim funding would be funded, during the interim period, at the proposed list price (as per the initial submission) as soon as practicable after the positive PBAC recommendation. A deed of agreement between the Sponsor and the Government covering the interim funding period would be required.

The timeline for this negotiation process could be mandated (for example 6 months from final cost-effective determination).

An independent arbitration or mediation mechanism may be needed to enable dispute resolution to break the deadlock when it happens (discussions/negotiations/price reconciliation with the DoHAC would be the 'first normal step' but if that fails, an independent process could find a resolution). In such a circumstance, the parties would agree to refer their dispute to a neutral tribunal. An arbitration tribunal has the power to make decisions that bind the parties.

Given that this is likely to be used in a very limited number of cases, there are existing avenues for arbitration, such as the Australian Disputes Centre, which offers commercial mediation as well as domestic arbitration. It has sample rules for both processes.

If arbitration is unsuccessful or PBS listing does not occur within the maximum duration for interim funding, the medicine is delisted under the existing arrangements for delisting.

An important consideration with interim funding is ensuring the **appropriate patient consent**. Informed patient consent would be required to demonstrate understanding that they are receiving a medicine under an interim mechanism.

Alternatively, for medicines with designated unmet clinical need and plausible benefit, or reimbursed overseas, automatic interim funding could commence before the HTA assessment is completed.

Issues related to this concept which require further consideration and discussion:

- Timelines for the interim funding period, including when it should start and end
- The nature of the deed of agreement between the Sponsor and the Government during the interim funding period
- Patient access during the interim funding period where the medicine is not yet on the ARTG
- Costing of the idea
- How central agencies should be accommodated.

B. Reform the HTA system to better enable first time success through the PBAC process

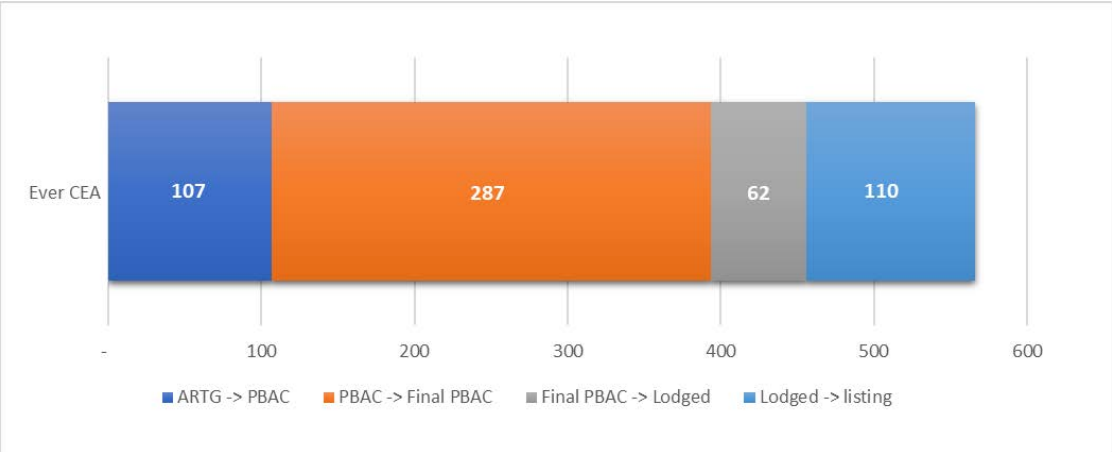
Q7 Recommendations – First time PBAC success

B. Reform the HTA system to better enable first time success through the PBAC process, by:

31. Frontloading the system through **earlier engagement**, including patient involvement.
32. **Streamlining the interactions** of the HTA Committees.
33. Introducing an **independent price negotiation process** to expedite access for certain medicines, to be mutually agreed.
34. Expand the current **independent review mechanism**, or consider an independent appeals process.
35. Ensuring there are **agreed, transparent metrics** for HTA processes to enable faster access.

As described earlier in this submission, resubmissions remain the greatest driver of delayed access for therapies with a claim of superiority to current treatment. An analysis of PBAC meetings, between March 2021 and March 2023 has shown that for most listings where a cost-effectiveness was used (implying a claim of superiority) the patient access gap is being driven by resubmissions to the PBAC and the post-PBAC listing process. The time from first PBAC meeting to final PBAC meeting took an average of 287 days – more than 9 months.

Figure 6: Patient* access gap (days) March 2021 to March 2023 with outlier removed



**PBAC recommendations leading to listing as of 31 May 2023 – outlier ARTG to 1st PBAC meeting 2131 days removed*

There are various ways to front-load the system in order to improve first time success at the PBAC meeting and minimise the need for resubmissions, or enable greater use of the early resolution pathway (where remaining issues could be easily resolved without the need for a full resubmission).

Front-loading the system through earlier engagement, including patient involvement

A scoping meeting or expanded PICO-type meeting

This would involve a meeting to establish the framework for evaluation for a cost-effective major submission and to reach broad agreement on the approach to the submission. (A similar approach is used in the UK's NICE scoping meetings.) Areas for consideration could include:

- The PICO evidence availability during the evaluation
- The planned approach to economic and financial modelling, identification of any key uncertainties or evidence challenges, risk-sharing arrangements and managed access programs (as relevant)
- Patient impact/benefits
- Utilisation.

The timing of the meeting could be flexible. In some instances there would be benefit in a Sponsor discussing the case prior to submission to the TGA to inform a decision on whether to proceed with a registration application. In other cases, there may be benefit in waiting until closer to the submission deadline if the readout of key data is being awaited that would inform the discussion.

Not all cases may warrant such a meeting and so the decision to include this step should be made on a case-by-case basis.

Attendees could include the Sponsor(s), DoHAC, evaluation group (identified early), PBAC chair and discussant(identified early), relevant colleges or clinicians, patient groups (PAGs), TGA representatives.

The outcome could be documented and form part of the submission with agreed advice on structure for PBAC review.

This idea addresses the following limitations of the existing pre-Submission meetings:

- Attended by Sponsor and DoHAC representatives only, and therefore lack input from patients, clinicians and decision makers.
- The meetings are relatively short (1 hour) leaving little time for in-depth discussion on any particular topic.
- Not a formal part of the HTA evaluation process.

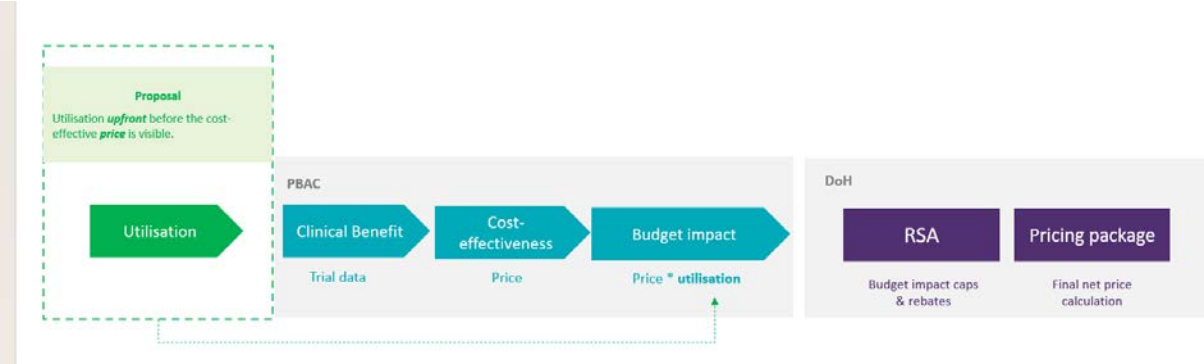
Issues related to this concept which require further consideration and discussion

- How early could such a scoping meeting take place?
- How would it be initiated?

<u>Early alignment on utilisation</u>

This idea is a less extensive proposal than (a). It focuses on utilisation, a key driver of budget impact and RSAs, and facilitates some independence between considerations of cost-effectiveness and budget impact.

Figure 7: Early alignment on utilisation



Issues related to this concept which require further consideration and discussion:

- Timing of the meeting
- Who should comprise the group that reviews utilisation?
- To what medicines should it apply?

Streamlining the interactions of the HTA Committees

Currently, PBS listing of medicines with a co-dependent technology that requires MSAC recommendation, vaccines (requiring ATAGI advice prior to PBAC submission), and drugs that require funding through the LSDP are particularly slow and complex. This is due to the involvement of multiple committees, and also due to much of the processing occurring in sequence rather than parallel.

There are examples of products having to wait an additional 4 months because of misalignment between the PBAC and MSAC.

The requirement for medicines eligible for the LSDP to be first rejected by the PBAC represents a barrier to timely access.

Case Study: PBAC and MSAC misalignment

Three submissions (tepotinib in NSCLC, larotrectinib for solid tumours and pembrolizumab for head & neck squamous cell carcinoma) missed out on being considered at the Dec 2021 intracycle PBAC meeting because MSAC meetings were not aligned with the PBAC intracycle meeting. These products had to wait an additional 4 months for a PBAC recommendation in March 2022.

The New Frontier Report included a recommendation that the HTA review consider and develop reforms in the following areas:

- Reducing the frequency and need for applications to HTA bodies to be resubmitted
- Streamlining the interaction between hospitals and the HTA system.
- Streamlining the interaction of the TGA, the PBAC, the MSAC and other HTA bodies.
- Cooperation and harmonisation between Australian Health Technology Assessment bodies and equivalent bodies overseas

Some possible ideas to address the interactions of HTA Committees are discussed in the following sections.

TGA and PBAC

Enable TGA and PBAC submissions to be submitted and assessed truly in parallel.

- Explore opportunities for direct communication between PBAC and TGA Delegate (and Sponsor) during TGA evaluation, enabling TGA and PBAC submissions to be submitted and assessed truly in parallel. Potential for development of joint regulatory and HTA evaluation of relevant data

PBAC and MSAC

Manage co-dependent submissions in a more timely fashion, or consider the PBAC assuming the role of both the MSAC and the PBAC for co-dependent submissions:

- Initially, PBAC to reconsider all deferred co-dependent submissions at the following PBAC intracycle meeting (ensure intracycle meeting between Nov & Mar), once the MSAC recommendation is available.
- Explore opportunities for the PBAC to assume the role of sole decision-maker for medicines with an associated technologies.

PBAC and ATAGI

Streamline the assessment and procurement of vaccines, to reduce overall burden and complexity and the potential for duplication of effort. Streamlining assessment can also increase transparency and person centredness. This has the potential to reduce the time to equitable and affordable access and to simplify the work needed to create access to vaccines, for Sponsors, evaluators and other stakeholders. Further, streamlining the assessment of vaccines can mitigate the real and increasing risk that cost-recovery for multiple assessments of vaccines is prohibitive for sponsor companies.

- Explore the opportunity for vaccines to be considered in a single evaluation, rather than sequentially by both ATAGI and PBAC.
- Explore streamlining (with KPIs) the post-PBAC and NIP tendering processes.

PBAC and LSDP

See separate recommendations on the LDSP in Chapter 3

Introduce an independent price negotiation process to expedite access for new medicines, to be mutually agreed

There is often disagreement during the PBAC evaluation process regarding the value of the medicines. MA believes the system would benefit from the introduction of a new process or oversight body, which could add value to governmental processes, improve decision making and accountability, and assist in achieving the appropriate balance between value-for-money reimbursement and ensuring sustainable supply. It could apply to specific cases where access needs to be expedited. The structure, objectives, operations and outcomes of the new process could be determined in dialogue between industry, government and other relevant stakeholders. Such a process could also consider the global context in which the industry operates.

Expand the scope of the current independent review mechanism, or consider the introduction of an independent appeals process

In the interests of greater transparency and accountability, as part of the US–Australia Free Trade Agreement, Australia agreed to establish a review mechanism that will be made available to an

applicant when an application to have a drug added to the PBS has not resulted in a PBAC recommendation to list[60].

The outcome of the independent review is considered by the PBAC. The outcome of the independent review is not substituted for the PBAC's decision.

In the almost 20 years that this mechanism has been available, it has only been used twice.

Consideration could be given to reviewing the barriers to use of the independent review mechanism, so that it can serve as a proper measure of accountability. For example, should the mechanism be extended to cover positive PBAC recommendations with conditions that provide no avenue for a Sponsor to move forward to listing?

Alternatively, consideration could be given to establishing an Independent Appeals process, akin to the Administrative Appeals Tribunal, the Commonwealth Ombudsman and the Veterans Review Board.

Providing such an appeals mechanism:

- Ensures that a factual basis for disputed decisions can be properly considered
- Ensures that independent analysis of facts can be undertaken
- Acts as a valuable management tool to assist Government agencies with feedback and quality control
- Ensures that proper reasons for recommendations are provided
- Improves the quality and consistency of Government decision-making.

[60] The relevant AUSFTA text is Annex 2-C which requires the Parties to

> *… make available an independent review process that may be invoked at the request of an applicant directly affected by a recommendation or determination.*

This is clarified in the associated Exchange of Letters that states that:

> *Australia shall provide an opportunity for independent review of PBAC determinations, where an application has not resulted in a PBAC recommendation to list.*

Ensure there are agreed, transparent metrics for HTA processes to enable faster access

Throughout this submission there have been recommendations around metrics and transparency: for ICER ranges (Recommendation 4) and time to access (Recommendation 6).

In addition, as discussed earlier in this chapter (**Figure 6**), the post-PBAC listing process is one of the key drivers of delays in access, taking almost six months.

The post-PBAC processes are less clearly defined than the other PBAC processes, particularly after a sponsor receives a positive recommendation from the PBAC and/or the MSAC to the time of listing. The streamlined pathways initiative introduced some timelines, however there are further efficiencies which could be introduced to reduce the time taken, including greater visibility of the process for Sponsors and clear metrics.

C. In addition to the above, ensure Australia is a first launch country

Q7 Recommendations – Australia is a first launch country

C. In addition to the above recommendations, ensure Australia is a first launch country, by:

35. Establishing **innovation incentives**.
36. **Exploring co-developed international work sharing**.
    - There are benefits to HTA bodies and industry from **international work-sharing for specific components** of assessments.
    - Industry seeks to **co-develop with the HTA bodies**, a framework that specifies the scope of joint assessments including information to be shared. This framework could be subject to periodic review and be informed by learnings from EUnetHTA.
    - Joint assessments should be **limited to cases where the Sponsor has opted in** and should be limited to products/indications where the PICOs align or have considerable overlap, as is the approach for the Access Consortium's New Active Substance Work-Sharing Initiative (NASWSI) and EUnetHTA joint assessments.

Establish innovation incentives

Failure to recognise and take account of the global nature of the pharmaceutical industry represents a barrier to the earliest possible access to medicines for Australian patients. Medicines research, development, manufacture, and supply are conducted globally and will only increase with further globalisation. This means that the market in Australia cannot, and does not, operate in isolation from the rest of the world. Global approaches are often applied to the medicines research, development, and market authorisation processes, as seen with trends towards globally harmonised regulatory systems, and work-sharing across international regulatory authorities. The frequency of this kind of global cooperation is increasing.

Medicines companies find it easier to accelerate timeliness for medicine launches when there is a high level of global harmonisation. Where there is a mismatch between the value placed on products and pricing in different countries there can be expected to be a difference in launch timing; in some cases, products may not be made available at all in some countries if the value attributed to them is lower than in comparable countries.

The Australian system needs to adequately consider the global context (and unintended consequences for global investment) when implementing local policy decisions, if Australia is to be a first launch country.

The impact of reducing attractiveness as a first launch country goes beyond the immediate impact on patients of delayed access, and includes:

1. Decreased incentive for global investment in conducting clinical trials in Australia
    - Reduced options for early access to innovative treatments for patients
2. Delayed regulatory submissions
    - Lack of incentive to use available TGA accelerated pathways (e.g. provisional approvals)
3. Decisions not to file in Australia
    - Reduced options for TGA to gain expertise or workshare with other comparable overseas regulators for ‘de novo’ evaluations of new innovative medicines and technologies and reducing their standing as a first-tier regulator
    - Resulting differences in standard of care due to available medicine options further reducing attractiveness of Australia for investment in clinical research as per the NZ model
    - Impact on generic/biosimilar medicine access pathways due to the absence of innovator medicines being registered in Australia

The HTA system affects the attractiveness of Australia as a first launch market through how medicines are valued, particularly the recognition of the innovation inherent in new medicines.

Policy settings in some countries recognise the value of innovation and provide incentives for such innovation.

For example, the Innovative Licensing and Access Pathway (ILAP) in the UK is designed to accelerate development and approval timelines for medicines, including new chemical entities, biological medicines, new indications, and repurposed medicines. ILAP will soon launch the HTA access forum tool to assist developers with upfront understanding of the value proposition of their product, fit in the current care pathway and practical and financial implications for product and service delivery. Eligibility for the ILAP is granted through the Innovation Passport designation, which is open at pre-clinical trial stage through to mid-development program. Designation is linked to the Target Development Profile and toolkit, which define key regulatory and development features and provide risk assessment and a strategic roadmap for achieving patient access.

Japan has an innovation premium which applies to therapies with new mechanism of actions, high efficacy or safety, or significant improvement in treatment. The premium ranges from 70–120%.

The concept of an innovation incentive is worthy of being introduced in the Australian context.

Explore co-developed international Work Sharing

As part of the HTA review, the Strategic Agreement will address: 'examining the feasibility of international work sharing for reimbursement submissions;' [5.3.2, MA Strategic Agreement].

It is understood the HTA bodies see international product-level work-sharing as critical to addressing their resourcing capacity challenges. A number of international collaborations have been established:

- An international collaboration arrangement involving Australia with five like-minded health technology assessment bodies in the UK and Canada. The agreement will allow the partners to work together on shared priorities to identify solutions to some of the common challenges they face. Five priority areas have been identified, including the topic of work-sharing and efficiency gains, in which partners will explore the feasibility of recognising or using each other's HTA information and explore running a pilot for a joint clinical assessment. This HTA collaboration will also likely seek learnings from ongoing regulatory collaborations, such as the ACCESS Consortium (Australia-Canada-Singapore-Switzerland-United Kingdom (Access) Consortium) and Project Orbis. Several products have been jointly appraised (dividing the labour) for regulatory review since the inception of these initiatives.
- The EUnetHTA collaboration has been developing product-level work-sharing processes across the EU, through the HTA Core Model®, which is a methodological framework for collaborative production and sharing of HTA information. The Joint Assessments (JAs) are

focused on the clinical assessment, excluding economic analyses and price negotiations. Cost and economic effectiveness are outside the scope of the work-sharing component of the HTA core model. The JA reports therefore focus on scoping the decision problem and conducting the clinical assessment, including indirect treatment comparisons where necessary. Cooperation in Europe will be further heightened with commencement of the Regulation on Health Technology Assessment (EU) 2021/228 in 2025.

Key considerations for international HTA work-sharing

- International collaboration in HTA clinical evaluations could lead to greater consistency and predictability in evidence requirements, leading to efficiencies for both HTA agencies and industry.
- Where the clinical decision problem is consistent between the countries (for example, the PICO are the same), joint assessment provides the benefit of a single submission and set of responses. Additionally, it is anticipated that the agencies would conform to a standardised approach to their assessment, providing greater consistency and predictability in interpretation of data
- If joint assessments include country-specific components, there is a risk of formal, or informal, price disclosure. This would be expected to lead to reduced flexibility in country-specific commercial arrangements and a net delay in access across the countries involved.
- Certain components of HTA analyses are country-specific. Countries have varying considerations of costs and cost-effectiveness, ethical & legal considerations, funding priorities and funding pathways. HTA clinical and economic analyses, and resultant 'value-based' effective prices, are thus tailored to each country. As a general principle, where analyses only pertain to an individual country, these should be out of scope for the joint assessment.

Appendix – Detailed analysis of international systems

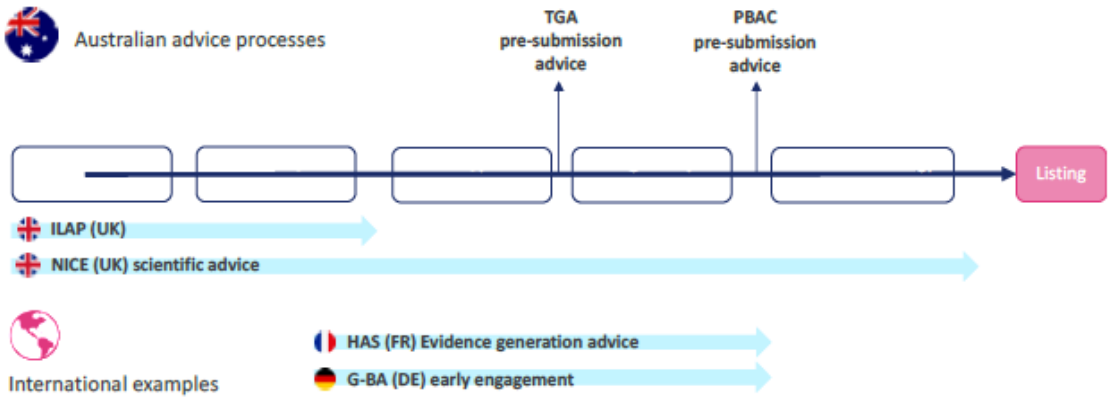
The following have been identified as key considerations for Australia in achieving the goal of reduced time between product registration and reimbursed access, with: alignment of access criteria to the indication on the regulatory label; flexibility for Sponsor-led submissions; and the ability for the Sponsor to define the reimbursed population.

1. Early engagement to work through important issues in evaluating the clinical and/or economic evidence

In terms of early engagement, markets like the UK and Germany dedicate a significant amount of resource years in advance to align with decision makers on the submission approach, compared with the Australian market where a pre-submission meeting is typically held about 3 months prior to submission lodgement with non-binding advice provided.

In other markets, the pre-submission advice is either binding or endorsed by the decision maker, giving the Sponsor greater certainty and predictability for the submission outcome and effectively front-loading a lot of the submission negotiation prior to lodgement.

Figure 8: Overview of Australian and international exampled of early engagement



Critical success factors in international systems

- Flexibility in engagement with the HTA body: for example NICE (UK) advice meetings have progressed to become more of a dialogue as compared to formal and restricted meetings held initially. This grants companies more flexibility for internal preparation and resourcing,

clarifying their "ask" and maximising insights from the agency at the start of and throughout the consultation process.[61]

- Appropriate timing and level of engagement to serve the objectives of the early engagement process, as well as follow-up after the advice has been received. For example, the Innovative Licensing and Access Pathway (ILAP) (UK) begins during early product development (prior to initiation of phase 3 pivotal trials).
- Seniority and experience of key individuals involved in early engagement, not only on the Sponsor side, but also within the HTA agency and experts advising the process, for a timely and efficient consultation process (noting that advice is always non-binding on the HTA outcome prior to full evidence review, although there could be some level of 'endorsement' by the HTA agency, as in the case of Germany). The appropriate level of authority for decision making should also be ensured when selecting representatives within the HTA agency.
- Resourcing within the HTA agency is sufficient to support national processes, and may also leverage/support international work sharing. Efficient resourcing should consider the potential to "'front-load'" a portion of the HTA process, such that any additional resourcing requirements are minimised, acknowledging that the costs of the PBAC submission process are recovered from industry.
    - Clearly defined procedures and eligibility criteria for specific programs/pathways e.g.:
        - Participation in ILAP (UK) is defined by three specific criteria, which provides clear guidance to product developers in demonstrating their eligibility for the Innovation Passport.
        - Early dialogue with Haute Autorité de Santé (French National Authority for Health) (HAS) (France (FR)) is structured as either a standard or accelerated procedure – detailed guidance on processes and timelines is publicly available for product developers.
- Integration with other initiatives: for example, principles and processes underpinning the ILAP (UK) were inspired by the Research to Access pathway for investigational drugs for COVID-19 (RAPID C-19). This was a multi-agency initiative which scans the research landscape for potential treatments, monitors trials, and evaluates the evidence and data via the National Institute for Health and Care Research (NIHR) Innovation Observatory. Research which shows clinical benefit and has acceptable safety profile is streamlined and prioritised for quicker access to patients.[62]

[61] Grueger J. Early Scientific Advice from Regulators and HTA: An Industry Perspective. ISPOR; 2015. Available from: https://www.ispor.org/docs/default-source/publications/value-outcomes-spotlight/january-february-2015/vos-the-industry-perspective.pdf?sfvrsn=80194d7b_2

[62] National Institute for Health and Care Excellence. Our role in the Innovative Licensing and Access Pathway (ILAP) [Internet]. UK: NICE; 2023. Available from: https://www.nice.org.uk/about/what-we-do/life-sciences/our-role-in-the-innovative-licensing-and-access-pathway--ilap

2. Accelerated Access: Provisional access pathway for products meeting certain eligibility criteria (integrated with the standard HTA system, focusing on areas of high unmet need, with re-review within a specified period) or immediate access for new, registered health technologies while HTA is conducted.

The UK and France provide good examples of accelerated access models. Patients in England can get early access to cutting-edge medicines through the Innovative Medicines Fund (IMF) which works like the Cancer Drugs Fund (CDF), fast-tracking promising treatments, even if they have not yet been approved for routine NHS use due to evidential uncertainty. The IMF and the CDF mean a newly approved medicine can be prescribed immediately, ensuring treatment can begin without delay and before NICE finalises its recommendations. Patients can access the treatment while data are collected for NICE to determine whether the medicine is affordable and effective enough to offer more widely. Since 2016, the CDF has provided earlier, time-limited access to promising new cancer medicines via managed access agreements, while further evidence is collected. This has benefitted over 80,000 patients who have been able to access 96 CDF-funded medicines treating 218 cancers. Since 2020, this concept has been extended to non-cancer medicines with the IMF[63].

In France, early access can be granted before marketing authorisation if the Autorisation d'acces precoce (AAP) finds evidence of a favourable benefit/risk ratio. Alternatively, the manufacturer may apply for early access after marketing authorisation, pending the standard pricing and reimbursement process. To be eligible for early access, a drug must meet certain requirements. Manufacturers must commit to making a medicine available to patients within 2 months of being granted early access and must submit an application for reimbursement within 1 month of obtaining marketing authorisation.

Critical success factors in international systems

- Mechanisms to manage total expenditures on the scheme and integration with standard HTA procedures, without top-down budget control measures, by applying eligibility criteria based on early cost-effectiveness modelling which have been the drivers of reforms to early/provisional access programs in the UK.
- Financial risk-sharing arrangements which provide clarity and certainty for both the Sponsor and Government, acknowledging that establishing a value-based price is challenging at this early stage. This may include parameters for agreeing prices, and transparency on any potential rebates that Sponsors may be responsible for. Adoption of clinically plausible assumptions in the economic evaluation, rather than only the most conservative assumptions, may assist in designing a risk sharing approach that may be acceptable to both the Sponsor and Government.

[63] National Institute for Health and Care Excellence. The Innovative Medicines Fund Principles. UK: NICE; 2022. Available from: https://www.england.nhs.uk/wp-content/uploads/2022/06/B1686-the-innovate-medicines-fund-principles-june-2022.pdf

- Clear eligibility criteria for therapies/indications, in order to target available resources to patients in areas of high unmet need (which includes the costs of patient access to therapy, program operations, data collection and monitoring). This may be linked to eligibility criteria for provisional marketing authorisation processes.
- Clear exit processes are required to facilitate transition from provisional access into a standard listing, which typically requires a re-review after a standard time period (for example, 2 years), and may result in price revisions and, potentially, delisting. In the event of delisting, arrangements must be in place for patients who are currently receiving treatment with the therapy.
- Future data requirements and how these will be incorporated into a re-review process should be clear for the Sponsor. Eligibility may include a data collection plan, considering ongoing clinical trials and/or RWE+ to resolve any remaining areas of uncertainty. Data collection plans are typically agreed ahead of entry into a provisional access program. This should include a clear, agreed protocol and/or well-defined research questions that the additional data is aiming to address.
- Data collection infrastructure may be required to enable RWE to be incorporated into a re-review of the product, which may be utilised to complement more mature clinical trial data that will be available at the time of re-review. RWE may shed light on the quality use of therapies in the local population.

Several countries enable patients to access new therapies (with marketing authorisation) before HTA is concluded. Examples of access available prior to full assessment include Austria and Germany. In Germany, the AMNOG process requires automatic reimbursed access once a drug receives marketing authorisation.

Critical success factors in international systems

- Mandated timelines ensure that the evaluation process occurs in a timely manner and that this is clear for the Sponsor, HTA agency, payer and other stakeholders .
- Interim pricing arrangements referenced to the comparator and/or other products within the broad disease area or clinical setting.
- Substantial early engagement between the Sponsor and HTA agency may be required while the product is still undergoing trials and marketing authorisation, such as in Germany.
- Integration with HTA, to ensure that an appropriate selection of products undergoes HTA and/or to enable smooth transition to full listing (or delisting) following HTA.
- Re-review process that may include delisting or price revision, following the completion of HTA, such that the final price and access arrangement reflects HTA principles.

3. Separation of pricing and contracting decision -makers from HTA

In France and Germany, any scope to negotiate price is determined based on an initial clinical benefit assessment level. Prices for products without benefit are referenced. The pricing authority is separate to the clinical review committee.

Critical success factors in international systems

- Clinical benefit assessment is the primary assessment tool, economic evaluation is secondary for products which are highly innovative and/or expected to have high budget impact, which means decision making is based on clinical factors primarily, not economic or pricing factors (e.g. Germany, France, and Japan).
- Separate bodies undertake the clinical benefit assessment and pricing negotiation, although pricing negotiations are informed (and constrained) by the clinical benefit assessment.
- Transparency and predictability in the pricing negotiation is enabled by defined 'buckets' of benefit for categorisation (in Germany and France), which set upper limits for the pricing negotiation.

4. Legislated time frames or KPIs for access

Almost all markets assessed have legislated or target timeframes for access. For example: Switzerland targets 60 days for reimbursement, following registration; England targets 90 days for guidance to be finalised, following registration; and Japan has a target for reimbursement within 60 to 90 days following registration.

Medicines for Rare Diseases

Medicines Australia also conducted international benchmarking for rare diseases (**Table 10**). It showed that there is no one model that addresses the complexity of HTA review. The review across selected countries shows that most have developed tailored processes to overcome the challenge of rare diseases, including aspects such as the introduction of supplemental processes, exclusion of cost-effectiveness analysis in HTA assessments or publication of higher or more flexible thresholds for funding.

Table 10: International benchmarking with a rare disease focus

Rare Disease Focus	Japan	Germany	Great Britain	France	Canada	Australia
Horizon scanning / joint Scientific Advice						
Rare Disease Policy and orphan definition	Yes	Yes	Yes	Yes	No	Yes
Early engagement, implementation planning	No	Yes	Yes	Yes	Yes	No
Pre-alignment on HTA parameters (eg comparator)	No	Yes	Yes	Yes	Yes	Partial
Regulatory approval						
Provisional reimbursement (for eg PhII data)	No	?		Yes	No	Yes
Parallel registration and reimbursement pathways	No	No	No	Partial	Yes	Yes
HTA priority pathway / fast track						
Rapid access for special circumstances	Yes	NA		?	No	Partial
Supplemental process for Rare or Ultra-Rare	Yes	Yes	Yes	Yes	No	No +LSDP
Access available prior to full assessment	Yes	Yes	Yes	Yes	No	No
Standard HTA / value assessment						
Flexible ICER threshold for RD/ use of QALYs	Exempt	PROM/ SF36	PROM/ EQ5D		Partial	Partial
Early & continuous stakeholder involvement	Yes	Yes	Yes	?	Yes	Partial
Patient perspective incorporated in value assessment	No	Yes	Yes	Yes	Yes	Partial
Broader value assessment beyond ICER	No	Yes	Yes	?	Yes	No
Pricing						
Separation of pricing decision maker from HTA	No	Partial		Yes	Yes	No
Initial free pricing period	No	Yes		Yes, at least	No	No
Statutory pricing adjustments to on patent medicines	Yes	Yes		?	?	Yes
Potential increases to maintenance price	No	?		?	No	No
Contracting						
Separation of contracting decision maker from HTA	No	Yes		Yes	Yes	No
Risk sharing beyond price-volume agreements	contracts	No	Yes	No	?	Partial
Single national registry for RD			Yes	Yes		No
Maximum budget/ volume threshold per RD medicine	Yes	Yes	Yes	Yes		No
Funding structures						
Centralised funding via national formulary	Yes	Yes		Yes	No	Yes
Private health insurance	Yes	Yes (10%)		Yes	Yes	No
Other						
Applicant led submissions	Yes	No		Yes	Yes	Yes
Clear timeframes or KPIs for access	Yes	Yes		Yes	Yes	No

Countries have adapted existing pathways or established supplementary pathways for orphan drugs

A review by Nicod et al[64] examined 32 countries for reimbursement pathways for rare diseases medicines and found 17 used standard HTA processes (with adapted features for orphan drugs) and 13 used supplemental processes. This indicates that no one system addresses the patient access gap for rare diseases, rather a 'fit for purpose' solution has been tailored to each country.

- The UK has a HST program for ultra-rare diseases. This pathway has a separate appraisal panel that includes rare disease experts. There are separate submission requirements and different value frameworks and willingness to pay (WTP) thresholds.

[64] Nicod E, Whittal A, Drummond M, Facey K. Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches. Orphanet J Rare Dis; 2020. Available from: https://ojrd.biomedcentral.com/articles/10.1186/s13023-020-01462-0

- Germany has a partially separate process where the appraisal committee is the same, but there are simplified evidence requirements and the absence of need for comparative data. An exemption from HTA assessment occurs if the medicine has a budget impact less than €50 M Euro.
- In France, orphan drugs go through the same HTA process, however the criteria for 'added therapeutic value' (ASMR) is considered met for orphan drugs with a budget impact of less than €30 M.

HTA submissions for rare disease indications are complex

The review across countries did not identify any country that had evolved HTA methods to suit rare diseases. Uncertain clinical effectiveness highlighted with HTA is a well-documented challenge for medicines for rare diseases. The uncertainty stems from gaps in knowledge of rare disease natural history, a patient pool insufficient to conduct adequately powered studies and a lack of disease-specific tools required to adequately describe quality of life or disability impact.

The recent NICE Methods Review from 2022 calls out reasons to be more flexible in HTA for rare diseases:

- Use of alternative quality of life measures to EQ-5D (4.3.11)
- Consideration of surrogate endpoints (4.6.7)
- Modelling parameters (4.6.28)
- Degree of certainty around value for money (6.2.34)[65].

The NICE RWE framework[66] also specifically calls out rare diseases as where RWE is potentially more relevant, due to the challenges in conducting high quality randomised controlled trials. Conducting RWE studies in rare diseases is also challenging, and the NICE RWE framework discusses options for designing and conducting RWE studies in rare diseases.

Pricing and contracting options are often used to address rare disease uncertainty

Reimbursement for orphan drugs is important for addressing access to treatment due to high cost of treatment at an individual level. There is insufficient information to compare pricing trends aspects across countries, however it is noted that there are trends in the countries reviewed for the collection of RWE for orphan drugs and the use of MAPs where funding is linked to outcomes.

[65] National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. UK: NICE; 2022. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

[66] National Institute for Health and Care Excellence. NICE real-world evidence framework. UK: NICE; 2022. Available from: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837

Alternative funding structures

It was noted that some European countries have a level of private insurance that supplements national formulary decisions. No information was found on the reliance of Sponsor access programs to help bridge the patient access gap between registration and reimbursement.

NHS England has recently announced the creation of a separately funded IMF. The program will fund qualifying treatments based on commercial negotiations and then be subject to HTA assessment. Patients with rare and genetic diseases are expected to benefit from this program.

Vaccine market access pathways: Comparison of markets

Austria, Canada, France, Germany, Japan, Switzerland and United Kingdom compared to Australia

Laigle et al.[67] considered vaccine market access (VMA) pathways across Europe and the United Kingdom. They identified key steps in VMA including horizon scanning, early advice, National Immunization Technical Advisory Group (NITAG) recommendation for inclusion in national immunisation programs, health technology assessment (HTA), final decision and procurement.

VMA pathways from this publication were extracted for Austria, France, Germany and the United Kingdom. To this Switzerland, Canada, Japan and Australia were added using the same methodology.

Table 11: **Vaccine market access pathways internationally** [68]

	Horizon scanning	Early advice	Initiation of assessment	NITAG recommendation	HTAB recommendation	Binding funding following final decision	Final decision/NIP inclusion	Procurement	Time to population access
Austria		Informal	MoH*	E(BI), Clin			N Lev	N Lev, R Lev	> 6 yrs
Canada			Spons	E(BI), E(CE), Clin			N Lev, R Lev	N Lev, R Lev	?
France	1 or 2 /yr	Formal		E(CE), Clin	Clin		N Lev	N Lev	< 2 yrs
Germany	1 or 2 /yr		NITAG	E(CE), Clin			N Lev	N Lev	< 2 yrs
Japan	?	?	?			?	N Lev		
*Switzerland**			Spons	E(CE), Clin			N Lev	N Lev, R Lev	?
United Kingdom	1 or 2 /yr	Informal	MoH*	E(CE), Clin				N Lev	< 2 yrs
Australia	Yes	Formal	Spons	Clin	E(CE), Clin		N Lev	N Lev	

*Can also be initiated by marketing authorization holder
Green-shaded boxes represent presence of step in the pathway
Clin, Driver: Clinical; E(BI), Driver: Economic, budget impact; E(CE), Driver: Economic, cost-effectiveness; HTAB, health technology assessment body; Local epi, Local epidemiology; MoH, Ministry of Health; NITAG, National Immunization Technical Advisory Group; N Lev, National level; PH, Driver: Public health; R Lev, Regional level; yr, year; Spons, sponsor; Time to population access: marketing authorisation to population access

[67] Laigle V, Postma MJ, Pavlovic M, Cadeddu C, Beck E, Kapusniak A, Toumi M. Vaccine market access pathways in the EU27 and the United Kingdom - analysis and recommendations for improvements. Vaccine; 2021. Available from: https://pubmed.ncbi.nlm.nih.gov/34404557/

[68] *Masserey Spicher V. The Federal Vaccination Commission in Switzerland: An officially appointed independent commission ensuring evidence-based recommendations and transparent procedures. Vaccine 28S (2010) A48–A53*

The VMA pathways for France, Germany and United Kingdom include horizon scanning as does Australia where companies have industry days with the Australian Technical Advisory Group on Immunisation (ATAGI) to discuss vaccines in development.

Early advice is obtained in Austria, Canada, France, United Kingdom and Australia, with only France and Australia being formal.

Initiation of the assessment is the Ministry of Health for Austria and the United Kingdom, the NITAG in the case of Germany and initiated by the Sponsors in Canada, Switzerland and Australia. This is not known for Japan.

The NITAG recommendation is driven by budget impact and clinical data for Austria; budget impact, cost-effectiveness and clinical data for Canada; cost-effectiveness and clinical data for France, Germany, Switzerland and the United Kingdom. For Australia, the recommendation from ATAGI is based predominantly on clinical data.

The health technology assessment body (HTAB) is only involved in France and Australia. The recommendation from HTAB for France is based on clinical data while the recommendation in Australia is based on cost-effectiveness and clinical data.

For most countries there is binding funding following the final decision.

Final decision/NIP inclusion is at a national level for all countries with the exception of Canada where it also occurs at the regional level. It is not an included step for the UK. Procurement occurs at a national level for all countries with the exception of Japan, Austria, Canada and Switzerland where procurement also occurs at a regional level.

France, Germany and the UK have time to population access of <2 years whereas it takes >6 years in the case of Austria. Timing is unknown for Canada, Japan and Switzerland.

For Australia time to access is variable. Both the ATAGI and PBAC timelines are well-defined; however, the tender stage can be lengthy.

The main difference between Australia and other countries, except France, is the recommendation from an HTAB. The NITAG makes recommendations based on cost-effectiveness in the case of Canada, France, Germany, Switzerland and the United Kingdom, whereas this determination is made by the PBAC in Australia. Therefore, all countries considered, except France, do not have a two-step (NITAG then HTAB) process, unlike Australia. This difference has implications for timelines and should be considered during the HTA review.

About Medicines Australia

Medicines Australia is the peak body representing the innovative, research-based, medicines industry in Australia. Our members discover, develop and manufacture medicines and vaccines that help people live longer, healthier lives and bring social and economic benefits to Australia.

Medicines Australia's members play a vital role in the health of the Australian economy and its citizens. Our members employ over ten thousand highly skilled Australians, generate billions in exports, and invest millions of dollars in research and development. Most importantly, this industry delivers medicines and vaccines that millions of Australians use every day to live longer, healthier, and more productive lives. Our members deliver innovative medicines and technologies nationwide that make a difference in people's overall health and wellbeing.

Pharmaceutical companies represented by Medicines Australia have a broad and deep pipeline of innovative medicines, diagnostics, treatments and vaccines. Our members develop, manufacture, and supply critical medicines and vaccines available on the pharmaceutical benefits scheme (PBS), the Life Saving Drugs Program (LSDP), the national immunisation program (NIP) and companion diagnostics or other treatments available through the Medical Benefits Scheme (MBS) and National Blood Authority (NBA). Our membership comprises small, medium, and large Australian and multi-national companies. Many of the world's multi-national medicines manufacturers are members of Medicines Australia through their local affiliates. These local affiliates provide a critical worldwide connection that enables Australians to access globally developed breakthrough medicines and therapies.