Optimising the availability and use of real world data and real world evidence to support health technology assessment in Australia

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This paper has been developed by members of the NHMRC Medicines Intelligence Centre of Research Excellence (MI-CRE).

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Disclaimer

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Glossary of terms

Commercial sector	The pharmaceutical industry, including sponsors requesting listing and commercial contractors who prepare submissions for listing on their behalf
Consumer and community representatives	Individuals or entities such as patients, carers, and families, who are not members or representatives of government, data stewards, the commercial sector, or data and methodology experts.
Data governance	Data governance are policies and processes to promote the availability, accessibility, quality and security of an organisation's data.
Data steward	Individuals or entities responsible for the quality, release, access, use and security of a dataset. Data stewards may also be referred to as data custodians
Health technology pipeline	A dynamic process through which health technologies evolve from concept development to clinical testing, regulatory and subsidy approval, and post-market surveillance
HTA lifecycle	An iterative process in which health technologies are assessed for subsidy, monitored and re-evaluated post-subsidy
Listing	Listing on the Pharmaceutical Benefits Scheme (PBS) or Medicare Benefits Schedule (MBS) for subsidy or reimbursement
PBAC	Pharmaceutical Benefits Advisory Committee. Responsible for health technology assessment in Australia
RWD	Real world data. Data collected during the routine delivery of health care
RWE	Real world evidence. Insights generated through the analysis of real world data (RWD)
TGA	Therapeutic Goods Administration. Responsible for regulation and market approval of health technologies in Australia

List of acronyms

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
APS	Australian Public Service
ARDC	Australian Research Data Commons
ARTG	Australian Register of Therapeutic Goods
ATMP	Advanced therapy medicinal products
CADTH	Canadian Agency for Drugs and Technologies in Health
CARE	Collective benefit, authority to control, responsibility and ethics
CDM	Common data model
CIOMS	Council for International Organizations of Medical Sciences
DARWIN-EU	Data Analysis and Real World Interrogation Network
DAT Act	Data Availability and Transparency Act (Australia)
DoHAC	Commonwealth Department of Health and Aged Care
DUSC	Drug Utilisation Sub Committee
EMA	European Medicines Agency
ENCePP	European Network for Centres of Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAIR	Findable, accessible, interoperable, reusable
FDA	United States Food and Drug Administration
HARPER	HARmonized Protocol Template to Enhance Reproducibility
HREC	Human research ethics committee
HTA	Health technology assessment
ICT	Information and communications technology
IHI	Individual Healthcare Identifier
ISPE	International Society for Pharmacoepidemiology
ISPOR	Professional Society for Health Economics and Outcomes Research
MADIP	Multi-Agency Data Integration Project
MBS	Medicare Benefits Schedule/Scheme
METeOR	Australian Institute of Health and Welfare Metadata Online Registry
MSAC	Medical Services Advisory Committee
NHDH	National Health Data Hub
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHSI	National Integrated Health Services Information data asset
NLP	Natural Language Processing
NMA	National Mutual Acceptance
OHDSI	Observational Health Data Sciences and Informatics
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme

PIA	Privacy Impact Assessment
PLIDA	Person-Level Integrated Data Asset
PREMS	Patient reported experience measures
PROMS	Patient reported outcome measures
RCT	Randomised clinical trial
RWD	Real world data
RWE	Real world evidence
TGA	Therapeutic Goods Administration
UK	United Kingdom

Executive Summary

Real world evidence (RWE), generated through the analysis of real world data (RWD), plays an important role in supporting the evidentiary needs of decision-makers across the health technology pipeline, including for market authorisation and subsidy approvals, as part of health technology assessment (HTA). This two-part report provides an overview of the current 'state-of-play' regarding RWD availability and access, and identifies opportunities for optimising the use of RWD and RWE to support HTA in Australia. It concludes with a series of high-level short-, medium-, and long-term steps to realise those opportunities. In particular, we focus on HTA for medicines and vaccines for listing on the Pharmaceutical Benefits Scheme (PBS) and related technologies for listing on the Medicare Benefits Scheme (MBS).

RWE development sits within the rapidly evolving global context of decision-making for regulatory agencies and payers. RWE has been used traditionally, and will continue to play an important role in HTA in estimating the incidence and prevalence of specific diseases, describing treatment landscapes before a health technology is listed, and in monitoring and surveillance after listing. In addition, there are three scenarios where RWD/RWE may be further leveraged, relating to the quality and availability of evidence from randomised clinical trials (RCTs) to support claims of (cost) effectiveness. These scenarios include where RCT evidence is deemed sufficient, not sufficient, or not available to support listing for reimbursement (Figure). RWE is being increasingly used in HTA for the latter two scenarios.

Scenario	Uncertainty	How can RWD be leveraged
1. RCT evidence sufficient	Do treatment effects translate to real world	Estimate real world safety & effectiveness Long-term safety Support expanded indications
2. RCT evidence not sufficient	Comparative efficacy (surrogate end-points, small sample sizes, inadequate follow-up)	Confirm safety and comparative (cost) effectiveness in real world settings
3. RCT evidence not available	Comparative efficacy due to lack of RCT control arm	Estimate rates of specific outcomes in usual care or for nominated active comparator (as an external control arm)

Figure: Scenarios where RWD can generate comparative treatment effects in HTA

Many new and emerging health technologies are likely to be used in highly select and very small patient populations (e.g., rare and ultra-rare diseases), with poorly characterised natural disease history, uncertain epidemiology, heterogenous phenotypes, and lack of diagnostic accuracy. As such, the key evidence uncertainties will likely fall into scenarios 2 and 3 in the figure above. The specific data needs to support HTA will depend on the type of therapy and the context in which it is being

used. International jurisdictions endorse the use of both quantitative and qualitative data in this context.

As is the case for other types of health technologies, applying a quality lens to RWD and the methods by which they are analysed is essential. We assert that the quality of RWE is multifactorial; it relies on the underlying data (provenance, reliability and missingness), the methods employed to analyse those data (appropriate study designs and analytic methods) and the question being addressed (are the data fit for purpose to generate the evidence required).

A framework supporting the integration of RWE in HTA decision-making in Australia is urgently required. Notable international initiatives, frameworks, and tools exist that could be adopted or readily adapted for Australian HTA to increase the quality and transparency of RWE to support the evidentiary needs of the Pharmaceutical Benefits Advisory Committee and the Medical Services Advisory Committee.

Australia has a wealth of traditional and emerging data sources that are or could be used to support HTA. A broad-ranging definition of RWD is recommended, that includes data collected routinely across health and social care, through disease- and health technology-specific registries, and directly from patients. While traditional RWD are primarily quantitative, qualitative data that incorporate patient-specific values and experiences will become increasingly relevant.

The existence of large volumes of data does not guarantee its timely use to support HTA; this report includes a comprehensive assessment of the barriers to RWD availability, access and use in Australia, with proposed solutions to roadblocks in access. Notably, the lack of transparency and harmonised streamlined pathways for data access remain a significant barrier for use of data in the context of HTA and broader uses including research.

Opportunities to maximise the value of RWD and RWE in Australia in the context of HTA are underpinned by four interconnected principles: partnerships, trust, data infrastructure, and methods. The table below presents options that could be feasibly adopted in Australia, and is designed to accommodate the rapidly evolving HTA, data, and methodological landscapes.

Table: Options to maximise the value of RWD and RWE for HTA in Australia

PARTNERSHIPS
Establish a multi-stakeholder advisory group, reporting to government, to co-design and oversee the development and implementation of enabling systems, pathways, evaluation, and research to optimise access and use of RWD in HTA.
TRUST
Develop a strategic approach to increase confidence, awareness, and acceptance of cross-jurisdictional and cross-sectoral RWD access and use in HTA. This approach should centre consumer and community engagement and co-design, leverage and integrate existing international activities

and guidelines, incorporate Australian context and evidence, and fine tune responses and messages specific to HTA. Critically, Australia should continue to develop and enhance systems that ensure privacy protections and data security.
DATA INFRASTRUCTURE
Develop a dynamic, enduring *whole-of-government* data infrastructure, including transparent and streamlined governance, that is fit-for-purpose to accelerate RWE development for HTA. This infrastructure should evolve over time, based on the needs of HTA agencies and other stakeholders. It should also be harmonised using international standards, be flexible to accommodate treatment landscape changes, scalable to incorporate emerging novel datasets, and allow transparent data quality assessment. Integrated health and social data from a *single* populous jurisdiction may be fit-for-purpose to address some research questions. These data may be more rapidly accessible and offer depth across multiple sectors.
METHODS
Develop a multi-stakeholder coordinated approach to transparent evidence development using best-practice methods for HTA, spanning data standardisation, standardised analytics, and reporting.

Part 2 of this report provides a roadmap to support these options, with a series of steps that can be taken immediately, within 12 months, and in the longer-term. Implementing the roadmap will require, in the first instance, efforts directed towards more harmonised, streamlined, and transparent ethics and governance processes for data access. This is the necessary foundational step to accelerating RWE development for HTA in Australia. Australia should also adopt a global perspective in its approach to generating robust evidence from local RWD. We endorse a co-ordinated, multi-stakeholder approach to this effort, to ensure long-term viability and the wise use of resources and infrastructure.

Background and Aim

The health technology pipeline is a dynamic process through which technologies evolve from concept development to clinical testing, regulatory and subsidy approval, and post-market surveillance. Real world evidence (RWE), generated through the analysis of real world data (RWD), plays an important role in supporting the evidentiary needs of decision-makers across the health technology pipeline, including for market authorisation and for subsidy approvals, as part of health technology assessment (HTA)[1]. RWD is defined by the International Network of Agencies for Health Technology Assessment as data collected during the routine delivery of health care[2], outside of clinical trial conditions. Other agencies and groups have more expansive definitions that also include data collected routinely across all aspects of health and social care, through disease and health technology specific registries and directly from patients through digital platforms[3, 4]. Real world evidence generated from RWD can provide policymakers with a more comprehensive understanding of the risks and benefits of health technologies in routine clinical care, which often differ to outcomes observed in randomised controlled trials (RCTs).

It is universally agreed that RCTs are the gold standard in establishing the efficacy of health technologies; estimates generated from RCTs have been the cornerstone of decision-making for regulation and HTA. However, it is also acknowledged that RCTs have limitations and, in some circumstances, are not possible to perform. While RWE cannot entirely replace the need for controlled experiments, it has demonstrated value, supporting the evidentiary needs of regulatory and HTA agencies globally. These agencies have long used descriptive RWE about disease epidemiology, treatment patterns, and burden of illness to support regulatory and subsidy decisions. They have also leveraged RWE to reduce uncertainty about the use and safety of health technologies once they are available for use in routine clinical care. RWE has also been used to assess the real world (cost) effectiveness and comparative (cost) effectiveness of health technologies; however, best practice methods and guidelines are still evolving in these domains. More recently, due largely to the development of health technologies for rare diseases, where clinical trials are not feasible or ethical, RWE has also been used to supplement clinical trials and estimate product efficacy.

In Australia, the regulation and market approval of new health technologies is the responsibility of the Therapeutic Goods Administration (TGA). The TGA assesses health technologies for their efficacy and safety before market authorisation and continues to monitor the risk-benefit balance of technologies in the post-market setting. Once market approval is granted the technologies are listed on the Australian Register of Therapeutic Goods (ARTG) at which time manufacturers or sponsors can apply to one of Australia's HTA committees for public subsidy; the TGA-PBAC parallel process allows some submissions related to medicines and vaccines to be evaluated by the Pharmaceutical Benefits Advisory Committee (PBAC) at any time after the lodgement of the TGA registration dossier. Two HTA advisory committees are relevant to this report. For medicines and vaccines, HTA is the responsibility of the PBAC. The Medical Services Advisory Committee (MSAC) appraises new and existing medical services funded on the Medicare Benefits Schedule (MBS) and other programmes. In scope for this report are health technologies that are considered by the PBAC or those under the remit of the MSAC that enhance the effect of health technologies listed on the PBS. These committees make recommendations to the Minister for Health for public subsidy (also referred to in

this paper as 'listing'). Subsidy decisions must consider both the benefits and harms of the health technology as well as the economic implications and impacts to the health system. These HTA processes support the sustainability, transparency, accountability, and independence of Australia's public funding system in a way that is consultative, flexible, and informed by 'robust and relevant evidence'[5].

The overall aim of this paper is to outline options for optimising the availability, utility, and use of RWD and the production of RWE to support decision-making across the HTA lifecycle in Australia.

This paper focuses on the use of RWD and RWE to support HTA for the PBAC and MSAC, in the context of the following health technologies:

- All medicines and vaccines
- Highly specialised therapies (such as cell and gene therapies)
- Other health technologies (for example a pathology test or an imaging technology) that improve health outcomes associated with the technologies defined above
- Foreseeable changes in health care that may influence the need, accessibility, effectiveness or cost-effectiveness of new health technologies.

This paper is divided into two interconnected parts, addressing the following issues:

- Part I: Real world data availability and access, and opportunities for use of RWD for assessments of health technologies in Australia throughout their lifecycles, including:
  - Key global developments in the use of RWD in HTA
  - Sources and types of RWD used to estimate the uptake and performance (assessment) of health technologies in Australia
  - Barriers and enablers of access to RWD for HTA in Australia
  - Sources and types of RWD that will be needed to estimate the uptake and performance of health technologies into the future
  - Opportunities to optimise the availability and use of RWD to support HTA in Australia.
- Part II: Roadmap for optimising the availability and use of RWD to generate robust RWE to support the HTA lifecycle in Australia, including:
  - A series of high-level short-, medium-, and long-term steps required to maximise the use of RWD to support HTA in Australia.

It is important to note, this paper is not:

- A systematic review of global RWE development
- An audit of real world data collections in Australia
- Horizon scan of new and emerging health technologies
- A synthesis of best-practice methods to generate RWE.

PART 1: Real world data availability and access, and opportunities for use of RWD for assessments of health technologies in Australia throughout their lifecycle

1. Methods

We developed a comprehensive search strategy to identify relevant published peer-reviewed literature across multiple databases, as well as grey literature and web content. We used a broad strategy as well as targeted strategies tailored to each of the topics. Table 1 summarises our general approach to identify key sources for inclusion.

Table 1: General approach to identify key literature sources

1. Web content of:
    - Regulators and payers in Europe, UK, North America and other jurisdictions
    - International Society of Pharmacoepidemiology
    - International Society for Pharmacoeconomics and Outcomes Research
    - Australian data stewards, linkage authorities and related government agencies.
2. Reference databases (PubMed, EMBASE) for literature on medicines, vaccines, cell and gene therapy and real world data in the context of health technology assessment. We restricted included literature to human studies, published from 2000 onwards. Indicative search terms included: biomedical technology assessment; health technology assessment; pharmaceutical preparations; prescription drugs; biological products; vaccines; genetic therapy; cell- and tissue-based therapy; reimbursement; financing, government; data collection; data base; real world data; product surveillance, post-marketing; information systems.
3. Review of reference lists from the sources identified in the points above.
4. Additional sources identified by key stakeholders.

We synthesised literature for the issues addressed in Part I according to the table on the following pages. Appendix A contains a list of references consulted for each of the issues.

Key global developments in the use of RWD and RWE in HTA
Synthesis: We identified the role of RWD and RWE in the context of the health technology pipeline, with a specific focus on RWE to support the HTA lifecycle. The scope of work specified the report identify the capacity of RWD to generate RWE in the following areas: • Consideration of new or amended subsidy or funding arrangements for health technologies, including: - estimating prevalence and predicting utilisation of new therapies and displacement of comparators - contextualising new therapies and associated health outcomes in the Australian setting (including determination of place in therapy) - contributing to the evidence-base to inform estimations of comparative safety, clinical- and cost-effectiveness. • Changing subsidy or funding arrangements after a medicine is subsidised or funded including through: - performance monitoring arrangements for health technologies subsidised under provisional arrangements (e.g., managed entry schemes or pay-for performance arrangements) - post-market review (including consideration of performance as well as newly listed alternative therapies, and/or indications which may change the relative safety and clinical- and cost- effectiveness). • Repurposing of existing health technologies (for indications not included in initial registered or funded indications). We undertook a more detailed synthesis of the use of RWD and RWE in the HTA lifecycle, incorporating the circumstances outlined above into this synthesis. We identified a series of scenarios relating to the availability and quality of RCT evidence to support claims of (cost) effectiveness. These are scenarios where RCT evidence is: sufficient, not sufficient, or not available. We also detailed the role of RWD in pre- and post-listing settings; the circumstances occur irrespective of the quality of RCT evidence.

Key sources and types of RWD used to estimate the uptake and performance of health technologies in Australia
Synthesis: We provided an overview of current, new and emerging Australian sources of RWD that can be leveraged to estimate the uptake and performance of health technologies. Specifically, we described RWD available to support evidentiary needs throughout the HTA lifecycle, including how the data are generated, their custodianship, and the capacity to link data at the person-level for specific purposes such as enriching data to obtain clinical information or confounding variables and obtaining outcome data.

Barriers and enablers of access to real world data for HTA
Synthesis: We identified issues arising from the peer-reviewed literature plus government and other multi-stakeholder consultations. We classified barriers into three broad themes: RWD availability, RWD access, and RWD use. We also documented actual or potential policy responses and enablers to the identified barriers.

Sources and types of RWD that will be needed to estimate the uptake and performance of health technologies into the future
Synthesis: We provided a general overview of the key sources and characteristics of RWD required to support HTA into the future, with specific regard to the assessment of highly specialised and co-dependent health technologies. We discussed the fit-for-purpose nature of data to address specific questions that may arise in the HTA lifecycle regardless of the health technology itself.

Opportunities to optimise the availability and use of RWD to support HTA in Australia
Synthesis: Finally, our synthesis of the four issues above informed our overview of the opportunities to optimise the availability and use of RWD to generate RWE that can support the lifecycle of HTA in Australia. The short-, medium- and long-term options to realising these opportunities are then presented in Part 2 of this report.

2: Findings

2.1: Key global developments in the use of RWD in HTA

Decision-making across the health technology pipeline is iterative. At each point decision-makers must assess whether the existing evidence addresses their uncertainties, fully or partially. Where significant uncertainty exists, new evidence must be generated; every time new information is generated, evidence gaps are narrowed or closed and/or new questions arise.

With the growth in access to, and linkage of, RWD across many disease areas and clinical settings, opportunities for RWE to both enhance and complement RCT evidence and support the evidentiary needs of decision-makers across the entire pipeline are evolving. The specific requirements for RWE differ across the pipeline according to the specific uncertainties, such as the efficacy of the technology given the clinical trial evidence or how the technology will impact the current healthcare landscape[6].

Use of RWD across the health technology pipeline

RWD and RWE have played an increasingly significant role in supporting decision-making across the health technology pipeline (Figure 1). Some of the key areas where RWE is used include:

- **Discovery:**
  - To better understand disease prevalence, progression, and characteristics of patients; to identify therapeutic targets based on observed associations between patient characteristics, disease outcomes and treatment responses.
- **Pre-clinical:**
  - To select patients with specific characteristics or disease profiles for pre-clinical studies.
- **Clinical:**
  - To help define clinical trial eligibility by characterising patient demographics, comorbidities and treatment histories; to help estimate clinical trial sample sizes based on variation in patient outcomes in routine clinical care.
- **Regulatory (Market Approval):**
  - To create external control arms for clinical trials, in situations where the use of traditional RCTs (with concurrent control groups) may be challenging, impractical or unethical.
- **Regulatory (Post-Market Approval):**
  - To monitor safety and effectiveness of health technologies after market approval.
  - To identify new safety signals or real world benefits.
  - To inform updates to labelling so they reflect additional safety information.
  - To expand approved indications to include new patient populations or conditions.
- **HTA (Subsidy Approval):**
  - To estimate real world comparative (cost) effectiveness of health technologies relative to standard of care or existing treatments.

- To generate inputs for (cost) effectiveness analyses by generating insights about real world resource use and associated costs.

- **HTA (Post-Listing):**
  - To input into clinical practice guidelines and benchmark guideline-recommended versus actual care.
  - To support continuous assessment of real world use, safety, (cost) effectiveness and economic impact of health technologies in diverse populations and complex, dynamic health care settings. This includes performance monitoring for health technologies subsidised under provisional arrangements (e.g., managed entry or pay-for performance) and in the context of newly listed alternative therapies (e.g., post-market review).
  - To evaluate the impact of subsidy changes on real world use and outcomes of specific health technologies.
  - To empower patients to make informed treatment choices using outcomes of patients with similar characteristics.

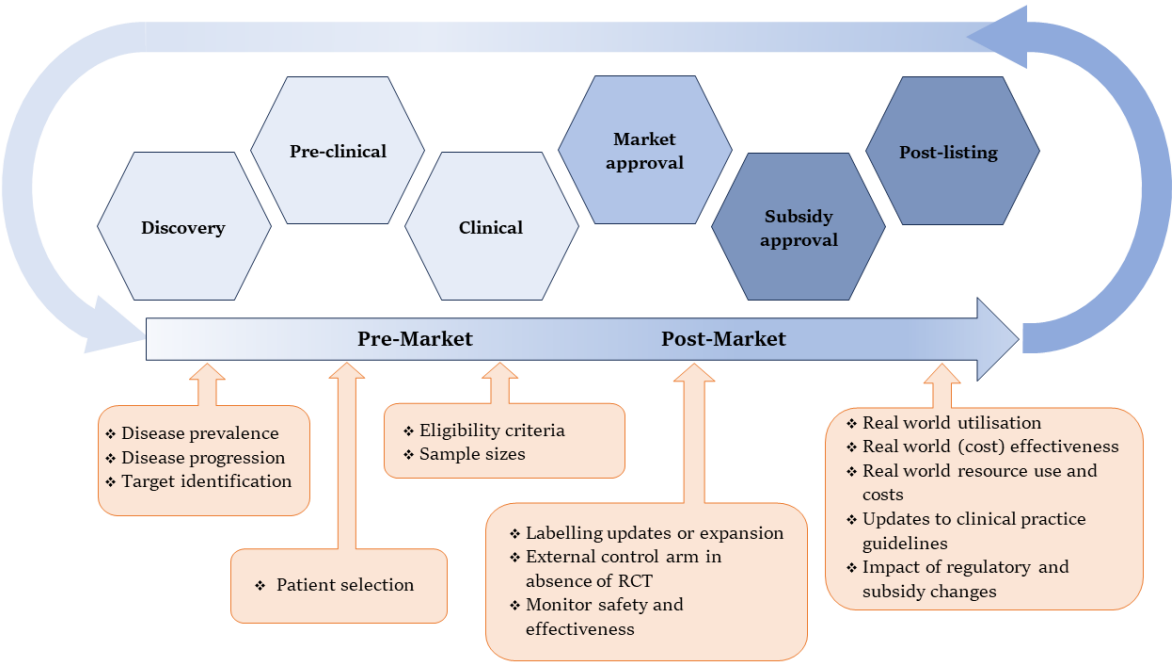

Figure 1: Applications of real world data across the health technology pipeline

Use of RWD in the HTA lifecycle

The previous section has provided a high-level overview of the place of RWD across the entire health technology pipeline. In this section we cover, in more depth and detail, the role of RWD in the HTA lifecycle, that is decisions around whether to subsidise a technology for reimbursement.

The foundational consideration for HTA relates to the comparative (cost) effectiveness of a health technology against standards of care or nominated comparators in the setting where the technology will be listed. Historically, pivotal estimates of comparative treatment effects have been generated in traditional RCTs. However, the completeness and quality of these estimates can be heterogenous. When there is uncertainty around the efficacy estimates established in RCTs, RWD is being used increasingly to establish the real world effectiveness of health technologies[7-9]. We have identified three scenarios where RWD may be of value to generate comparative treatment effects in HTA (Table 2).

Table 2: Scenarios where RWD can generate comparative treatment effects in HTA

SCENARIO 1: RCT evidence is sufficient at the time of listing
Occurs when comparative treatment effects are well characterised in RCTs, i.e., appropriate comparison/placebo group and validated endpoints. In this scenario, the health technology is recommended for full listing. **RWD can be leveraged to:** • Monitor characteristics of real world treated patients compared to trial populations. • Estimate real world safety and effectiveness of health technologies outside of clinical trial conditions, in patient populations not tested in clinical trials. • Assess appropriateness of assumptions regarding longer term outcomes, beyond the scope of the RCT, to generate insights into the performance of the health technology over an extended period. • Support the expansion of subsidised populations into patient groups outside those included in RCTs. RWE usually takes some time to accumulate after the subsidy decision. RWE can help to inform price negotiations or changing subsidy and funding arrangements after a technology has been subsidised where effectiveness in the real world is found to be different to that expected from clinical trials or where alternative therapies and/or indications may change the relative safety and clinical- and cost- effectiveness. RWE can also be used to support the repurposing of existing health technologies for expanded indications.
SCENARIO 2: RCT evidence is not sufficient at the time of listing
Occurs when RCT evidence is available, however significant uncertainties remain about the efficacy of health technologies. This scenario is likely when RCTs: use surrogate endpoints, involve small sample sizes, have limited power to detect treatment effects, and inadequate

follow-up. In addition, uncertainty arises when the treatment setting or inclusion criteria of the population are different to the expected real world use of the health technology. In this scenario, the technology may be recommended for listing under specific conditions requiring additional evidence post-listing to address areas of uncertainty (e.g., as part of a managed entry scheme or as a conditional listing).

RWD can be leveraged to:

- Confirm safety and comparative (cost) effectiveness in real world settings, in the longer term, or where surrogate or modelled outcomes were used in RCTs.

RWE is usually required within a discrete time frame, during a conditional listing period, to satisfy ongoing funding conditions. RWE can support the conversion of the technology to full listing, and support performance monitoring arrangements for health technologies subsidised under conditional arrangements (e.g., managed entry schemes or pay-for-performance arrangements). Once fully listed – RWE can support HTA as per Scenario 1.

SCENARIO 3: Comparative RCT evidence is not available

Occurs when there is no evidence of the comparative effect of the technology against standard of care or a nominated active comparator at the time of the listing. This occurs because there is only a single arm trial or there is no RCT data available for the nominated comparator. This scenario is common when assessing the effectiveness of health technologies in areas of high unmet need, in rare/ultra-rare diseases (e.g., in molecularly defined disease or cancers with specific genetic mutations), when urgent access is required (such as for COVID-19) or in situations when RCTs are unethical, not feasible or impractical given limited patient populations. In this scenario, the technology may be either fully or provisionally listed.

RWD can be leveraged to:

- Estimate rates of specific outcomes in usual care or for the nominated active comparator.

RWE is required prior to listing to contribute to the evidence base to inform estimates of the comparative safety, clinical- and cost- effectiveness of technologies. For example, RWE can provide external control arm data for single arm trials. Once technologies are listed RWE can support the post-listing effectiveness monitoring requirements as detailed in Scenario 1 for fully listed technologies or Scenario 2 for conditionally listed technologies.

Irrespective of the quality, comprehensiveness, or availability of comparative (cost) effectiveness estimates for a health technology, there are a series of other RWD inputs required to inform and monitor subsidy decisions. In the *pre-listing* HTA phase, RWD can help to describe the clinical context where the health technology will be used, and support decision-makers to estimate the overall economic impact of the technology should it be listed. These inputs are used in the consideration of new subsidy arrangements for health technologies to estimate prevalence and predict utilisation of new therapies and displacement of comparators. In the *post-listing* phase, RWD

can be used to monitor the utilisation and impact of technologies after they have been subsidised. These estimates in the post-listing space are required as inputs in the ongoing assessment of the overall costs in the post-listing (cost) effectiveness calculations and may result in policy responses such as changes to funding restrictions and price negotiations. Applications of RWD across the pre- and post-listing phases are listed in Figure 2.

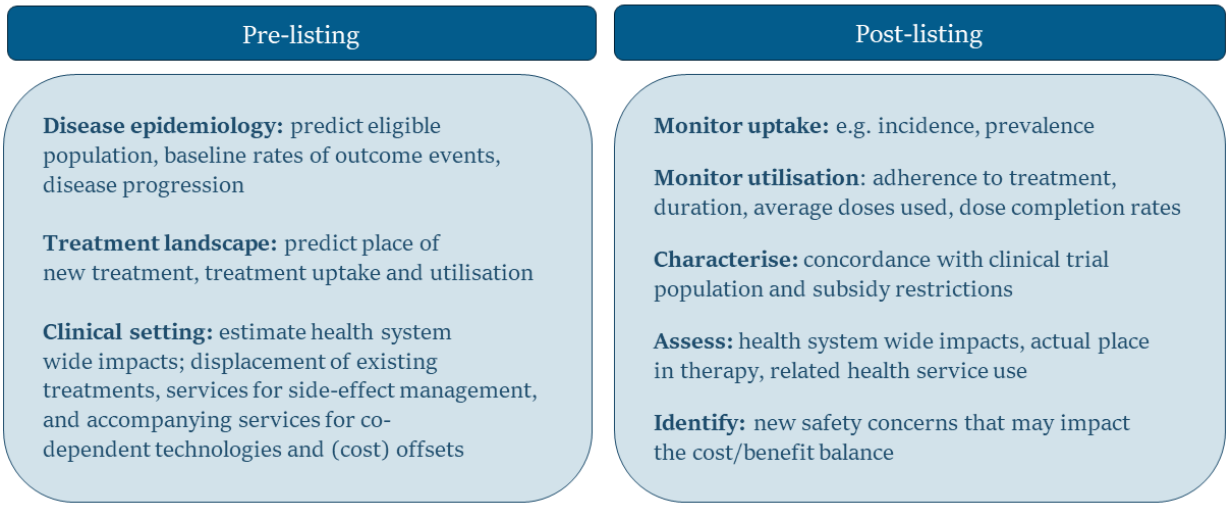

Figure 2: RWD inputs to inform and monitor subsidy decisions

Assessing quality of RWE

The acceptability of RWE for HTA is often hindered by questions relating to quality. RCTs are considered the highest quality evidence in demonstrating the efficacy of a health technology as they are designed to address a specific study hypothesis or question, randomisation is used to ensure that bias and confounding is minimised, data are collected purposefully, and data curation is highly regulated. In contrast, studies leveraging RWD, where data is commonly collected in real world clinical settings, are subject to bias and confounding and may not have complete capture of all necessary information.

The quality of RWE is multifactorial: it relies on the quality of the underlying data (provenance, reliability and missingness), the quality of the methods used to analyse those data (appropriate study design and analytic methods to control for bias) and the quality of the question itself (data fit for purpose to address the question).

Many of the RWE frameworks developed by HTA bodies specifically address the quality of the data and the methods used to generate the evidence. Issues relating to data quality considered by these frameworks include[3]:

1. Data relevance (availability, representativeness):

a. Selecting appropriate data sources that can adequately address the specific study question in terms of the study population, availability of exposure(s), outcomes(s) and key covariates that are required to address potential confounding.
b. Assessment of data provenance, quality of the data accrual process, quality of the data linkage processes.

2. Data reliability (accuracy, completeness):
    a. Data quality including potential for missing data, and curation of the final analytic dataset.
    b. Development, validation and verification of algorithms used to define key study elements such as definitions of exposure (e.g., medicine initiation), study outcomes (e.g., phenotypes for the occurrence of a medical event of interest) and key study covariates.

Many of the large-scale international data collaborations have designed Data Quality Assessment frameworks that support the assessment of real world data for use in RWE, such as the Khan Data Quality Assessment Terminology and Framework for Secondary use of EHR Data[40].

Issues relating to the quality of the methods used include:

1. Use of appropriate study design.
2. Analytical methods to minimise bias due to confounding.

There are multiple guidance documents for conducting RWE studies that address these issues, including the Council for International Organizations of Medical Sciences (CIOMS) – Working group XIII: Report on Real-World Data and Real-World Evidence in Regulatory Decision Making[18] and the European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP): Guide on Methodological Standards in Pharmacoepidemiology[19].

Global frameworks and guidance on RWE development

Recognising the increasing importance and application of RWE across the health technology pipeline, regulatory agencies and HTA bodies worldwide have formally endorsed the use of RWD and RWE to support their evidentiary needs. Many of these organisations have developed RWE frameworks outlining where and how RWE is, and could be, used. A number of notable RWE frameworks relate to regulatory decision-making, however the principles they address are applicable in the context of HTA. There is no universally accepted RWE framework, with each organisation accounting for their local health technology and data landscape plus the roles and functions of the respective organisation. As such, there is variation between organisations in the application and acceptance of RWE. Below, we detail two notable frameworks, one from a regulator and another from an HTA agency.

In 2020, the European Medicines Agency (EMA) published their 'EMA network strategy to 2025'[10], identifying opportunities to leverage health data across the EU for better regulatory decisions. The strategy acknowledges that:

- Clinical trials remain the foundational method for establishing safety and efficacy of medicines.
- RWD can fill important evidence gaps, particularly at market authorisation and in the post-authorisation phase.
- RWE can complement clinical trials for technologies used to treat rare diseases (i.e. where comparative clinical trials are difficult to perform).
- RWD can generate RWE for regulatory and HTA decisions including natural history of disease and use in populations not included in clinical trials.
- RWE has an established role in monitoring safety in the post-authorisation phase and there is growing interest in the use of RWE to monitor product effectiveness, within indication and in populations not tested in clinical studies (i.e., population subgroups typically excluded from clinical trials such as paediatric populations and pregnant women).
- Developing analytical capabilities, new data analytical methodologies and digital tools is fundamental to generating robust RWE.

The EMA's RWE Framework highlights that fostering collaboration with key external stakeholders with the requisite competencies and capabilities is critical to the integration of RWE for regulation and HTA[11]. As such, in early 2022, the EMA launched the Data Analysis and Real World Interrogation Network (DARWIN-EU®), a partnership with academic researchers, coordinated by Erasmus University Medical Centre. DARWIN-EU supports the generation and use of RWE for disease estimation, population characterisation, and estimation of the use and performance of medicinal products. DARWIN-EU is establishing a standardised catalogue of real world healthcare databases across the EU and developing standardised best-practice tools for using those data, to provide timely and reliable evidence of the safety and effectiveness of medicines and vaccines.

In 2022, the UK's National Institute for Health and Care Excellence (NICE) published their Real World Evidence framework[4]. The framework supports the NICE strategy 2021 to 2026, to use real world data to 'resolve gaps in knowledge and drive forward access to innovations for patients'. The framework identifies opportunities for RWD to reduce uncertainty and improve guidance and describes best practice for the implementation of RWE studies including planning, conducting, and reporting to improve quality and transparency of the resulting evidence. NICE recognises RCTs as the preferred evidence source for measuring the effects of interventions, but recommends the use of RWE in circumstances where RCT evidence is not sufficient including when[4]:

- RCT comparators do not reflect standard of care in local settings.
- Relevant population groups are excluded from RCTs.
- Major discrepancies exist between RCT and routine practice.
- Follow-up is limited, surrogate outcomes are used or RCTs are poor quality.

NICE also endorses RWD to[4]:

- Characterise health conditions.
- Estimate inputs for economic models.

- Develop and validate digital health technologies.
- Understand health inequalities.
- Monitor safety.
- Assess impacts of health technologies on service delivery.
- Assess applicability of RCTs to patients in the National Health Service (NHS).

NICE anticipates that the routine use of RWD in any of the circumstances cited above would translate to expedited patient access. As in the EMA strategy, the enabling conditions for RWD to become an effective part of the UK HTA pipeline are the availability of high-quality fit-for-purpose data and the use of best-practice, high-quality and transparent RWE studies that address key risks of bias.

While aspects of individual RWE frameworks differ between agencies, most are consistent in their endorsement of best-practice methods and transparency of reporting to enhance trust in decision-making. These standards, developed by professional societies and academic researchers, recommend registration of standardised study protocols, reporting against checklists, reporting on data quality and integrity, openly publishing algorithms and analytical code, and the use of best-practice methodology. The specific RWE standards also vary across organisations[12]. Examples of key methodological standards for RWE generation published by regulatory agencies, scientific organisations and professional societies include:

- Reporting to improve reproducibility
    - Joint International Society for Pharmacoepidemiology (ISPE) / Professional Society for Health Economics and Outcomes Research (ISPOR) Special Taskforce on Real-World Evidence in Health Care Decision Making: HARmonized Protocol template to Enhance Reproducibility (HARPER) Guidelines[13]
    - Canadian Agency for Drugs and Technologies in Health (CADTH): Guidance for Reporting Real-World Evidence[14]
    - Real-World Evidence Transparency Initiative (partnership between ISPOR, ISPE, Duke-Margolis Center for Health Policy, National Pharmaceutical Council): good practices for establishing a culture of transparency around the conduct and reporting of real world studies testing hypotheses about comparative effectiveness or safety [15-17]
- Best-practices for conduct of RWD studies of treatment and/or comparative effectiveness
    - Council for International Organizations of Medical Sciences (CIOMS) – Working group XIII: Report on Real-World Data and Real-World Evidence in Regulatory Decision Making[18]
    - The European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP): Guide on Methodological Standards in Pharmacoepidemiology[19]
    - EMA: Guideline on registry-based studies[20]

2.2: Sources and types of RWD used to estimate the uptake and performance (assessment) of health technologies in Australia

RWD have been used for decades to generate evidence across the health technology pipeline with many data types already widely accepted and embedded in decision-making[21]. RWD is an all-encompassing term referring to heterogeneous information generated from a variety of sources. As detailed above, RWD is defined by the International Network of Agencies for Health Technology Assessment as data collected during the routine delivery of health care[2], outside of clinical trial conditions. However, more expansive definitions are emerging as RWD and RWE development are maturing. They include data collected routinely across all aspects of health and social care, through disease and health technology specific registries and directly from patients through digital platforms[3, 4]. We endorse the use of a more expansive definition of RWD.

As RWD are collected in real world settings, they can have whole-of-population coverage or may represent select populations or subgroups. As the capacity to link heterogeneous data at the person level has increased, it is now more feasible to bring together disparate RWD collections thus enhancing the uses of these data to support HTA. Many existing taxonomies classify traditional and emerging sources of RWD that can be leveraged to support RWE generation in the context of HTA[3, 4, 7, 8]. We have developed our taxonomy of data sources (Table 3), through the lens of RWD available in Australia; we also provide key examples of data types for each source.

Table 3: Current, new, and emerging data sources and types of RWD for estimating the uptake and performance (assessment) of health technologies in Australia

ADMINISTRATIVE: Collected by governments and other organisations about their operations for administrative and reimbursement purposes
• Claims • Claims for services, including visits to health practitioners, pathology and imaging services • Hospital separations • Emergency department visits • Private health insurance claims • Residential aged care services • Mental health conditions and services • Disability diagnoses and services • Government benefits (social security payments and use of social services) • Income and taxation • Migration, visa and settlement • Sales of health technologies (medicines) to suppliers (pharmacies)
ELECTRONIC HEALTH RECORDS: Diagnostic and procedural data collected by health practitioners and payers at the point of care for clinical management
• Primary care (including presenting symptoms and signs, prescriptions including dose, indication for medicine use, treatment outcomes, family history, body mass index, smoking status, alcohol consumption)

• Other specialist care (including indication for medicine use, prescribed dose, presenting symptoms and signs, family history, body mass index, smoking status, alcohol consumption) • Pathology/histology/microbiology results • Hospital discharge and progress summaries • Radiology images and results • Allied health care, including dental and optometric
REGISTRY: Clinical, diagnostic and/or procedural data collected and notified by health practitioners or organisations, often under mandate
• Fact and cause of death • Birth • Immunisation • Clinical Quality Registries • Disease, including rare diseases • Medicine, device • Cancer screening
SURVEYS: Self-reported quantitative or qualitative information relating to demographic, behavioural, medical, and social circumstances of patients and perspectives from other stakeholders
• Patient reported outcome measures (PROMS) • Patient reported experience measures (PREMS) • Medical history • Family history • Disability, including type and severity • Health-related behaviours (e.g., smoking history) • Measures of socio-economic status (SES) including income, employment, occupation, educational attainment, and health insurance status • Ethnicity and other measures of cultural and linguistic diversity • Other social determinants of health (e.g., housing type) • Patient diaries
MOLECULAR: Diagnostic and other biological data collected by health practitioners
• Genetic and genomic • Multi-omics (proteomics, transcriptomics, metabolomics, lipidomics) • Other biomarker status, including tumour markers (e.g., receptor status of breast cancers; HPV status of head and neck cancers)
MOBILE: Clinical data collected by a third party outside of formal health care delivery environments, either continuously or repeatedly
• Activity and body function (i.e., blood pressure, heart rate, glucose levels) measurements from wearables, implants and other devices

CASE REPORTS: Voluntary reports completed by patients, health practitioners and industry (sponsors)
• Spontaneous adverse event reports related to medicine or vaccine use
SOCIAL MEDIA: Publicly posted data on health outcomes, preferences, and health-seeking behaviours
• Social media platforms

Each data source has distinct advantages and disadvantages. Importantly, the vast majority of data used in the context of HTA is for a 'secondary' purpose, outside of the primary purpose for which they were first collected. The primary exception here is data collected from patients as part of the HTA process itself.

Administrative data, collected by governments and other organisations about their operations for administrative and reimbursement purposes, have long-standing utility in the HTA lifecycle. Administrative data generally have whole-of-population coverage (e.g., for persons eligible for various government programs). Social administrative data collections can complement health data and can be used to monitor the uptake of health technologies in special populations (e.g., by socio-economic strata or ethnicity) or can be used for confounding control in causal inference studies. However, these routinely collected data do not contain detailed clinical data or diagnostic data, meaning that proxies for medical conditions and diagnoses must be inferred, and there is no specific information on disease subtype or severity.

Electronic health records contain diagnostic and procedural data collected by health practitioners and payers at the point of care for clinical management. They rarely have population-wide coverage, often focusing on settings in selected regions or areas. As these data are collected at the point of care, usually through electronic clinical record systems, these data include non-standardised terminologies, unstructured data fields and are vulnerable to missing data. Electronic health records are useful for identifying standard of care, assessing use of health technology in practice, and potentially identification of comparison groups when RCT evidence is absent.

Registries contain clinical, diagnostic and/or procedural data collected and notified by health practitioners or organisations, often under mandate. They are often established for surveillance of a specific disease or health technology and collect standardised information from treating health care professionals and patients. The coverage, completeness and quality of these data is highly variable. Moreover, registries established around a specific health technology only include consenting patients or those who do not opt out of the data collection. Registry data may be used to estimate disease prevalence (e.g., whole-of-population registries) and to generate control arm outcomes for comparative effectiveness if the standard of care treatment is on the market or if there is no treatment available.

Surveys are also useful for collecting data on select populations who consent to provide their data (except for the Census which is generally compulsory). The value of survey data is that, like some administrative data, it can be used for confounding control in causal inference studies (e.g., health status, medical history, ethnicity, etc), for monitoring health technology use in special populations

(e.g., by socioeconomic status or ethnicity), or to supplement outcome data (e.g., PROMS and other self-reported functionality data). Survey data is not only a source of efficacy data (e.g., patient reported outcome measures), but is also critical to assess post-market utilisation of health technologies in 'untested' populations. Qualitative data can also provide valuable insights for decision-makers. Australian HTA bodies are committed to understanding and integrating consumer perspectives, and those of other stakeholders including clinicians into their decision-making.

Molecular data – that is, diagnostic and other biological data collected by health practitioners – are increasingly necessary to estimate the prevalence of rare and ultra-rare diseases and disease subtypes. The value of emerging data sources such as mobile, case reports and social media data remains uncertain. These data are likely to have potential for certain diseases and health technologies but require validation prior to use for HTA.

Some examples of key RWD sources for HTA in Australia are outlined in Appendix B. Most high-value RWD sources are linkable and thus in scope for inclusion in cross-sectoral integrated data assets. It will be imperative that these high-value datasets are critically and transparently appraised, including the data linkage process, to ensure they are of high quality and valid for decision-making.

Current uses of RWD in HTA in Australia

RWE has been used traditionally, and will continue to play an important role, in the pre- and post-listing setting. For example, Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS) claims have been used routinely for many decades to monitor the uptake and costs of subsidised health technologies[22-24] and disease registers and routine data collections are leveraged to estimate the incidence and prevalence of disease. Consumers and other stakeholders can provide their views about a specific health technology under consideration by the PBAC and MSAC via a Department of Health web portal. These qualitative comments are synthesised by the consumer members of the respective committees and are provided to the committees at the time of product assessment. Increasingly RWE is being used in HTA when RCT evidence is not sufficient or is not available when assessing claims for (cost) effectiveness (scenarios 2 and 3, Figure 2). For example, RWD has been used to provide external control arm data for single arm trials. Currently, there are no pre-specified frameworks regarding the presentation or quality assessment of RWE provided in submissions. Rather, assessment relies on the expertise of assessors and committee members critiquing the submissions. Other HTA bodies internationally are developing and requiring such frameworks (see *Global frameworks and guidance on RWE development on p21*). Harmonising Australia's approach to the generation of RWE to be consistent with international standards will assist in a more rapid, consistent, and streamlined use of RWD for the purpose of HTA.

Bringing disparate data collections together

As there is no single data source that contains all the information required to support HTA, linking data sources at the person level can help to maximise the value of the broad array of data now available in Australia. Importantly for HTA, data linkage can help to bring together data on health technology exposures (e.g., PBS data) and key assessment outcomes (e.g., fact of death, cancer notifications or hospitalisation events), as well as data that can contribute to control for bias and confounding. For example, prospective cohort studies and Clinical Quality Registries, that collect

detailed information on patients, have been linked to routine data collections such as state based hospital separation data to enrich outcome assessment and support long-term follow-up of their populations, and MBS and PBS claims which can be leveraged to better adjust for confounding factors in studies of health technologies.

Over the last two decades, Australia has invested in infrastructure to enhance our capacity to link data using best practice privacy preserving protocols. We now have numerous accredited data linkage units supporting (within-jurisdiction) Commonwealth and state/territory linkage activities with a subset also auspiced to perform cross-jurisdictional linkage between Commonwealth and State-based collections. Population spines, whereby data collections are nationally representative as opposed to disease- or health-service specific, are essential for numerous RWE needs.

Enduring population-wide data linkages, which are updated and maintained on a routine basis and not tied to a specific population or scientific question of interest, have the ability to play a critical role in RWE development sustainability and feasibility for HTA in Australia. A number of enduring linkages are currently in development by the Australian Bureau of Statistics (ABS) and the Australian Institute of Health and Welfare (AIHW), although at the time of writing, access to these data is limited to specific stakeholder groups. Some of these collections are integrating individual-level health and social data which is highly valuable in the context of HTA as this can be used for confounding control in causal inference studies (e.g., health status, medical history, ethnicity, etc), and for monitoring health technology use in special populations (e.g., by socioeconomic status or ethnicity). In Appendix B we list some key sources that have capacity, due to data linkage with administrative or electronic health records, to be useful for HTA in Australia.

Leveraging multiple linked data collections for HTA

RWD are collected for different purposes, meaning database structures are heterogeneous in terms of design, formats, and terminologies. Common data models (CDMs) harmonise and standardise these different structures into a single system. There are many advantages to using a CDM, including the capacity to pool multiple data sources into one unified data set (whether those data are physically brought together in the same analytic environment (centralised) or remain in situ (distributed)), thereby enabling larger sample sizes, broader patient populations, and more rapid large-scale analytics. Transforming and mapping heterogeneous data sources to a common data structure enables the conduct of large-scale studies across multiple jurisdictions, nationally and internationally.

CDMs are in routine use globally by various collaborative networks to support regulatory and HTA activities. Various networks and CDMs exist including: Observational Health Data Sciences and Informatics (OHDSI), US FDA Sentinel, the National Patient-Centered Clinical Research Network (PCORnet®), the Canadian Network for Observational Drug Effect Studies (CNODES) and the Data Analysis and Real World Interrogation Network (DARWIN EU®). These networks are critical in the context of rare and ultra-rare diseases, as data from multiple jurisdictions are often required to explore specific research questions in these relatively small populations. The main advantage of a CDM is that analytics can also be standardised which enables faster and more efficient use of those

data. The use of CDMs is growing in Australia but they are not used routinely, either in the context of HTA or for other purposes.

2.3: Barriers and enablers of access to RWD for HTA in Australia

In this section and in Tables 1-8 in Appendix C we summarise seminal Australian and international documents and literature relevant to the Australian HTA context[4, 6, 18, 24-36]. Several documents used in this synthesis arise from government and other consultations that have engaged a broad number of stakeholders including government, the research sector, commercial sector, and consumer and community representatives. **We classified the barriers into three broad themes: RWD availability, RWD access, and RWD use.** We also synthesised information cited in the documents around policy responses (actual or potential) and enablers to the identified barriers.

Many of the barriers and enablers we have identified cut across our three themes, highlighting the potential impact and efficiencies that could be (or are being) realised through their resolution. Moreover, many of the challenges and solutions are not confined to HTA and reflect the broader Australian data ecosystem. An overarching HTA framework could achieve the collaboration, principles, regulations, designs, structures, and productivity necessary to address current and future challenges.

Australia should look to the lessons learnt from mature RWD systems in other jurisdictions. Although no two data systems are the same, successful RWD systems all have key common elements:

- data governance is streamlined and transparent,
- there are cultures of continuous improvement and investments in data quality and interoperability,
- access and use of the data for health system planning and evaluation is separate from use for research, and
- use (and linkage) of different types of data is encouraged.

Barriers and enablers to RWD availability in Australia

Barriers to RWD availability in Australia span legal, socio-cultural, and organisational areas.

Legal

Legal impediments to data sharing remain a primary barrier to maximising use of RWD and require further enabling legislation and a whole-of-government approach. Cross-sectoral linkage, access and use of data for HTA and related activities such as RWE methods development (i.e., research), must be explicit. An absence of, or lack of clarity about, consent for sharing and reusing certain data types for HTA, is also a barrier. This is especially relevant to private sector datasets and some Clinical Quality Registries and electronic health records. The development and widespread adoption of guidance for obtaining (opt-out) consent, in conjunction with a targeted communication plan addressing societal trust, may increase the availability of datasets with enriched clinical and socio-demographic information.

Socio-cultural

Concerns about data privacy and security are barriers to increasing the availability of RWD for HTA and other purposes in Australia. These societal concerns arise from a lack of confidence and trust in data protections because of high-profile and impactful data breaches involving the release of identifying information, and unease about the potential for misuse of data, both of which have occurred outside of the linked data setting. Relatedly, there is an expectation by some that informed consent must be obtained for the sharing and reuse of personal (health) information.

Several actions could strengthen and maintain the social license for expanding RWD available for RWE generation in Australia. They include conducting and publishing comprehensive Privacy Impact Assessments (PIAs), generating Equity Principles for the access and use of RWD, and designing and implementing an overarching evaluation framework and workforce strategy. Central to public trust is transparency about the risks and safeguards in the RWD infrastructure, the place and public value of RWD/RWE in HTA, and the system for generating RWE. Strategically co-designing communication materials with stakeholders, especially consumer and community representatives, will have the greatest positive impacts. Ongoing research to understand public sentiment and people's information needs, and the factors they take into consideration when considering data sharing, is also enabling. Other facilitators include involving patients in the process of determining questions that can be addressed by RWD/RWE and involving patients in the generation of data.

Another socio-cultural barrier to RWD availability is non-acceptance of RWE by some HTA stakeholders. Several co-designed and coordinated activities could ascertain and allay those concerns and help realise the inclusion of emerging and new high-value datasets in the RWD pipeline.

Organisational

Data governance, or the policies and processes to promote the availability, accessibility, quality, and security of an organisation's data, is both a barrier and an enabler to RWD use in Australia and globally. Harmonisation of data governance across all levels of government is a critical first step that would generate significant efficiencies across the public sector and for all RWD stakeholders.

Data stewards play a pivotal role in data availability for RWD research in Australia. Data stewards (may also be referred to as data custodians) are responsible for the quality, release, access, use and security of a dataset and can represent government, academic or the commercial sectors. Apart from legal barriers, the obstacles to data stewards agreeing to share their data can be summarised as: insufficient knowledge about requirements for consent for data sharing, data sharing safeguards, and governance frameworks; low trust in some data users; inadequate resources; and insufficient incentives to share. These barriers could be overcome with guidance and education customised for data stewards and data users, cross-sectoral partnership and collaboration, the adoption of transparent research practices, and a federated data infrastructure that is resourced to support the enduring integration of datasets of significance to HTA.

There are also operational and technical barriers to RWD availability for HTA and other purposes in Australia. As discussed above, Australian RWD, expertise, and stakeholders are siloed. Furthermore, data fragmentation is the result of the Australian model of healthcare delivery; exposure data is

collected and governed separately from outcomes data. There is no comprehensive catalogue of RWD sources that can be used for HTA; although we have named some examples (see Appendix B), a scoping review could discover and prioritise datasets of significance to HTA across the spectrum of exposure, covariate, and outcome data.

Other major operational barriers to RWD availability include the prohibitive costs associated with collecting high-value RWD, as well as the costs and time required for data quality assurance and curation. A cost-sharing approach, with contributions by all the beneficiaries of HTA in Australia, could be explored. Contemporary data are essential to HTA decision-making; however, key outcome data, such as death and cancer notifications, often face significant lags in availability. Independent interrogation of the RWD pipelines and workflows underpinning these vital RWD assets could also yield actionable efficiencies. Technical barriers to data access include lack of data interoperability and standardisation, and a suite of steps under a national data strategy could help to mitigate them.

Barriers and enablers to RWD access in Australia

Whilst several barriers to RWD access have been ameliorated to some extent in recent years, there remain substantial impediments to equitable RWD access by third parties outside of government and some other data stewards (e.g., some Clinical Quality Registries), hindering its potential utility for HTA.

The AIHW National Integrated Health Service Information (NIHSI) Analysis Asset, a major national enduring linked data asset encompassing exposure and outcome data, could be leveraged to support a broad suite of HTA activities. However, the asset has only recently been opened to non-government researchers and thus the governance requirements and application pathway are untested. The application costs are unpublished (at the time of writing), and there are major gaps in the available state and territory hospital and emergency data that significantly limit its utility. The ABS PLIDA/MADIP, a longitudinal data asset combining exposure, Medicare services, education, government payments, income and taxation, employment, and population demographic data, has significantly more advanced governance requirements and a mature business model compared to previous frameworks. However, the asset includes only narrow health data (i.e., does not contain hospital records for diagnosis or outcome ascertainment) and therefore currently has limited utility for HTA. Outside of these two enduring linked data assets, the governance requirements for researcher RWD access lack transparency and are onerous. There remains appreciable scope for further unification, simplification, and digitisation of the data governance and ethical review arrangements. Furthermore, there is a significant need for First Nations-led pathways for access to data about First Nations people, and the outcomes of the APS-wide Framework for Indigenous Data and Governance are widely anticipated[41].

The commercial sector does not currently have access to many of the Australian linked data sources listed in Table 3. Enablers include clear and reasonable guidance, requirements and processes, cross-sectoral partnership, collaboration and investment, and access to fit-for-purpose RWD. Commercial sector access to RWD to support HTA applications could lead to innovation and accelerated patient

access to new therapies. However appropriate safeguards against private monetisation of the data and use for other purposes is required.

Australia could adopt the common, tested features of mature RWD systems in other jurisdictions, including centralised and distinct entities managing linked data access, and transparent data governance and data sharing agreements. This approach would enhance equity of access. The governance framework must be centred on the national interest yet allow for strong controls (sign-off) where requested by data stewards.

Barriers and enablers to RWD use in Australia

Commercial sector

There is a strong desire within the commercial sector (i.e., industry, sponsors and contractors) to incorporate RWD/RWE into decision-making across the health technology pipeline, including building 'regulatory-grade' synthetic control or comparator groups, designing adaptive trials, understanding the heterogeneity of treatment effects, informing label revisions related to product safety, and informing pricing. The commercial sector is investing in RWD/RWE systems in-house and in partnership.

The commercial sector has identified specific barriers to their RWD use in Australia. These barriers include uncertainty about the RWE evidentiary needs of Australian regulators and payers, lack of guidance about how they should apply and weigh RWE in their regulatory submissions, a lack of end-to-end RWE capability, uncertainty regarding the Australian RWD/RWE strategy and their place in it, and the risk of their commercially sensitive information entering the public domain.

Data-related

The data-related barriers include inadequate information about RWD quality, representativeness, and utility, inadequate RWD standardisation, and gaps in the available RWD. For example, RWD gaps prevent the accurate identification of cohorts with ultra-rare diseases and the generation of robust historical comparator groups. These data information needs could be addressed via high-quality metadata and synthetic data, and cross-sectoral collaborations and research to identify and reduce data uncertainties. Improved RWD standardisation could occur at the point of data collection or prior to analysis, including through transformation to an international Common Data Model. Cross-sectoral partnership working groups could prioritise existing and new data collections to address the RWD gaps. Common features of successful, mature RWD capabilities internationally are worthy of consideration and include systems and processes that foster continuous improvements in data quality and interoperability. Longer-term, the availability of a single digital patient record[37] would offer significant value to HTA in Australia.

Organisational

The primary organisational barrier to use of RWD is uncertainty in the robustness of the RWE, and relatedly, inadequate methodological transparency and RWE reproducibility, and the use of inappropriate statistical methods. A lack of coordinated investment in methodological standards for

different activities across the RWE pipeline limits the quality and scope of RWE generation. An end-to-end HTA data infrastructure and RWE workforce that supports and requires transparency and evaluation is a key enabler.

Non-government researchers also face excessive charges to use RWD in secure remote environments, highlighting the need for true cost-recovery business models and potentially cost-sharing approaches. There is scope for creative institution-level approaches across RWD infrastructures that minimise accounting costs and maximise productivity. There needs to be greater awareness and protections against the potential for harm that may occur to communities reported on in the RWE generation (e.g., First Nations people, culturally and linguistically diverse populations, people with disabilities, marginalised communities, and many others), and this could be achieved through a suite of organisational measures across the HTA system, the centrepiece of which is co-research with communities. Multiple barriers could be addressed by establishing a cross-sectoral RWD/RWE partnership and implementing a coordinated national workforce strategy.

2.4: Sources and types of RWD that will be needed to estimate the uptake and performance of health technologies into the future

Predicting the future of health technologies is challenging, due to the rapid pace of innovation and uncertainties surrounding their development. While it is beyond the scope of this paper to undertake horizon scanning in this area, many future technologies are likely to be advanced therapy medicinal products (ATMPs). These innovative health technologies often involve complex and personalised approaches to treatment.

The European Medicines Agency (EMA) places ATMPs into three categories:

- **Gene therapies:** involve the introduction, alteration or removal of genetic material within patient cells to treat or prevent disease. They target inherited genetic disorders, acquired diseases and some types of cancer. Gene therapies are classified as somatic or germline therapies. Somatic therapies aim to correct genetic defects or introduce genes into specific tissues and organs. They target cells not passed on to future generations. Germline therapies modify genetic material in reproductive (egg or sperm) cells to prevent the transmission of disease to future generations.
- **Cell therapies:** involve administration of living cells to patients to treat disease. They can be autologous (from patient) or allogeneic (from a donor).
- **Tissue engineered products:** involve the combination of cells or biomaterials to create functional tissues or organs or to facilitate tissue regeneration.

Definitions of these therapies vary by jurisdiction. For example, The US FDA classifies similar health technologies as 'gene therapy products', 'cellular and gene therapy products', and 'human cell and tissue products.'

ATMPs are expected to bring important health benefits to populations with high unmet medical needs, for conditions deemed highly challenging or previously untreatable. However, ATMPs have high degrees of uncertainty with respect to safety and efficacy; they also pose unique challenges regarding manufacturing, regulatory and subsidy approvals, due to their personalised and complex nature. Many of these technologies will be used in highly select and very small patient populations (e.g., in rare and ultra-rare disease), with poorly characterised natural history of disease, uncertain epidemiology, heterogeneous phenotypes and lack of diagnostic accuracy. In these situations, it is unlikely that comparative technologies will be available to establish comparative effectiveness. Despite these significant uncertainties, the unit cost of treatment is very high. In addition, companion diagnostics (e.g., medical tests or assays) are often required to identify patients most likely to benefit from treatment based on their unique genetic, molecular or biochemical characteristics. In the context of rare and ultra-rare diseases, companion diagnostics also play a critical role in optimising treatment outcomes. The heterogeneity of these diseases means a one-size-fits all approach to treatment may not be suitable or effective.

The key HTA uncertainty scenarios regarding the comparative effectiveness of ATMPs will fall into Scenario 2 or 3 detailed above (Figure 2). This is due to the high-level of uncertainty around long-term claims, as clinical trials will not address life-long outcomes, and because comparative

effectiveness of these health technologies will be difficult to assess in RCTs as identifying appropriate comparators will be challenging[9]. A key opportunity for the use of RWE for the assessment of ATMPs will be to estimate outcome rates in standard-of care treatments and other relevant interventions to benchmark outcomes of ATMPs.

As health technologies evolve so too will the data needed to assess them. The HTA of ATMPs will require comprehensive RWD to evaluate the safety, efficacy, (cost) effectiveness, and broader impact of these innovative therapies. ATMPs often have long-lasting effects, so long-term follow-up data on exposures and outcomes to understand the durability of treatment effects, late-onset adverse events, and patient outcomes over an extended period will be crucial. Importantly, however, acceptance of RWD in HTA decisions among HTA authorities is high for these more challenging situations[9, 38].

The specific data needed for HTA of ATMPs will vary depending on the type of therapy and the context in which it is used (e.g., hospital versus community practice). Like other health technologies, leveraging data on resource use and costs (including hospitalisations, doctor visits and co-dependent technology and other health interventions) will be critical. Due to the uncertainty of outcomes for these treatments, patient-generated data such as patient-reported outcomes and patient stories will be fundamental to establishing the anticipated or actual real world impact of these therapies, and appropriate analytical developments including Natural Language Processing (NLP) of unstructured free text will be required to analyse those data collected. Detailed clinical and therapy-specific data will also be necessary, including condition- or health technology specific- registers with pre-specified standardised data collection plus biomarker data to monitor therapeutic response and evaluate outcomes. Importantly, these data will also need the capacity to link with routine data collections to improve operational efficiency for long-term evaluation. As novel and innovative data are accessed for HTA it will be important that these data are subject to rigorous quality assessment (see *Assessing quality of RWE* on p19). Furthermore, collaboration with data custodians and researchers with expertise in those datasets will be necessary to ensure appropriate methodologies are utilised.

Pressure, on the part of patients and health care professionals, to make these technologies accessible and affordable will mean that, at the time of listing, there will be a high degree of uncertainty about the use and performance of these technologies in routine practice. RWE will be critical in supporting and verifying claims made at the time of initial listing.

The Canadian Agency for Drugs and Technologies in Health (CADTH) recently undertook a multi-stakeholder consultation and developed guidance to optimise the integration of RWD and RWE in HTA decision-making for treatment for rare diseases[39]. These insights are highly relevant and applicable in the broader context of future health technologies. They encourage early and iterative multi-stakeholder dialogue to identify the data required to reduce uncertainties. They include collecting data on:

- What is a clinically meaningful change for patients and caregivers: incorporating their values, preferences, unmet needs, key milestones and burden on caregivers. These data may be both qualitative and quantitative in nature.
- Disease-based outcomes, rather than technology-specific outcomes.

- Comparative value of new technologies using data generated from single-arm studies and epidemiological data from the local context concerning natural history and/or burden of disease.
- Important subgroups such as patients not included in trials and special populations (e.g., First Nations people).
- Quality of life using standardised measures.
- Economic outcomes (e.g., health resource use data, cost-effectiveness, and cost-utility).

The CADTH review also identified specific issues around the use of data across the Canadian data ecosystem that equally apply to the Australian context. They suggest:

- Using data from existing disease-based registries to augment or complement existing information from other data sources (e.g., administrative data).
- Leveraging existing data sources, data linkage infrastructure, and expertise (e.g., health care resource utilisation data, claims data, industry and private datasets, electronic medical records, chart reviews, and other hospital data).
- Leveraging international registry data and published scientific literature.
- Collaborating with multiple stakeholders to develop national registries: either one national rare disease registry (with both common and disease-specific data elements) OR disease-specific registries that can be accessed through a single national platform.

2.5: Overview of the options for Part 1 of this paper: Opportunities to optimise the availability and use of RWD to support HTA in Australia

Using the findings above, we have summarised the current state-of-play with respect to enhancing RWD availability and use in Australia around **four core interconnected principles: partnerships, trust, data infrastructure, and methods**. These principles align with those developed by Capkun et al[6] (policy and partnerships, trust, data, and methodology). First, we describe how these principles apply to the current use of RWD in Australia in the context of HTA. Next, we identify future opportunities to improve the current situation. Specific options to realise these opportunities are presented in Part 2 of this report.

Table 4: Principles to optimise the availability and use of RWD for HTA in Australia

PARTNERSHIPS
Current situation
Australia has a wealth of RWD that could be used to generate RWE for HTA. However, the Australian RWD infrastructure is fragmented. Use is reactive to specific ad-hoc questions as they arise, and access is hampered by lack of coordination across different siloed stakeholders. Communications between stakeholder groups are generally bilateral rather than coordinated. There is a general lack of transparency around metadata, protocols, methods, and reporting. Consumer engagement is embedded in HTA processes and goodwill and strong relationships exist. There is cross-sectoral agreement that systemic barriers to data use and access must be addressed; there is a high readiness for change.
Opportunity
Australia could establish an advisory group, reporting to government, to co-design and oversee the development and implementation of enabling systems, pathways, evaluation, and research to optimise access and use of RWD in HTA. This should be a multi-stakeholder, collaborative advisory group including but not limited to consumers and other stakeholders from government, the commercial sector, academia and research sector, and data stewards.

TRUST
Current situation
Society and culture / social license: there is a lack of understanding in the broader community about the use of RWD for public benefit. In particular, there is a distrust in the use of RWD by government and the commercial sector due to issues of data quality and integrity, data reliability, methodological transparency, validity and potential for bias and confounding. Highly public

breaches of identifiable data have a negative impact on public perceptions of digital data safety and security.

Data (HTA-specific): the nature of HTA is such that many of the circumstances where RWD are leveraged to support decision-making are in 'commercial-in-confidence' documents that are not public facing. Public summary documents relating to PBAC or MSAC decisions are limited in detail and do not routinely feature estimates derived from RWD. The exception to this are reports from the Drug Utilisation Sub Committee (DUSC) of the PBAC and the post-market surveillance team (i.e., DUSC Utilisation Analysis Public Release Documents). Critically, access to RWD for HTA is dependent on non-uniform data steward policies. While almost all key data collections are publicly funded, many data stewards restrict access; the commercial sector is particularly disadvantaged in this regard.

RWE: there has been a pervading view that observational evidence based on RWD is not of sufficient quality in the context of HTA. While confidence is increasing through greater transparency, and the development of frameworks for RWE generation and reporting by key regulatory bodies and international societies, some groups remain sceptical about its utility, particularly in relation to causal inference.

Opportunity

Australia could develop a strategic approach to increase confidence, awareness, and acceptance of cross-jurisdictional and cross-sectoral RWD access and use in HTA. This approach should centre consumer and community engagement and co-design, leverage and integrate existing international activities and guidelines, incorporate Australian context and evidence, and fine tune responses and messages specific to HTA. Critically, Australia should continue to develop and enhance systems that ensure privacy protections and data security.

DATA INFRASTRUCTURE

Current situation

Australia has invested heavily in infrastructure to facilitate access to RWD. Consequently, there is a large and growing infrastructure of linked data collections that have utility in the context of HTA. Legislation is also in place to facilitate access to Commonwealth data for public benefit. However, there is no systematic integration of data that is fit-for-purpose for HTA, and the growing infrastructure is fragmented, not harmonised, nor standardised in a way that facilities timely access (with the exception of the ABS PLIDA/MADIP). There is also inequity of access based on sector and budget. With the exception of the PBS 10% sample dataset (whereby license arrangements are managed by Services Australia), there is also a lack of transparency around pathways to data access, so RWD utility and feasibility for HTA is uncertain.

Opportunity

Australia could develop a dynamic, enduring *whole-of-government* data infrastructure, including transparent and streamlined governance, that is fit-for-purpose to accelerate RWE development for HTA. This infrastructure should evolve over time, based on the need of HTA agencies and other stakeholders. It should also be harmonised using international standards, flexible to accommodate treatment landscape changes, scalable to incorporate emerging novel datasets and allow transparent data quality assessment.

METHODS
Current situation
There is a general lack of transparency of methods that are, or could be, used across the RWE development lifecycle. Activities and effort are siloed, there is marked heterogeneity in the application of best-practice methods and a lack of guidance and skills in RWE generation specific to Australia. Mature systems have evolved internationally, accompanied by toolkits and templates.
Opportunity
Australia could develop a multi-stakeholder coordinated approach to transparent evidence development using best-practice methods for HTA, spanning data standardisation, standardised analytics, and reporting.

PART 2: Roadmap for optimising the availability and use of RWD to generate robust RWE to support the HTA lifecycle in Australia.

We have developed a roadmap that could be feasibly adopted in Australia to realise the opportunities detailed in the previous section. The roadmap is underpinned by four principles: partnerships, trust, data infrastructure, and methods. We have generated a series of high-level steps that can be accomplished in the immediate term, within 12 months, and longer term. These options will need to be realised to maximise the use of RWD to support HTA in Australia, including requirements for system sustainability such as resourcing, funding, and policy commitment.

Australia currently has an important opportunity to build a comparative advantage over other countries given our universal health system, growing digitisation, and existing data infrastructure. However, cross-jurisdictional and cross-sectoral partnerships are required to establish a sustainable, safe, flexible, and cost-effective infrastructure that maximises the Australian capability for RWD/RWE for HTA. The key to the success of this roadmap will be a transparent framework guiding the use of RWD/RWE for HTA in Australia that is collaboratively designed and developed by all relevant stakeholder groups. This will require trade-offs to achieve change for national benefit.

PARTNERSHIPS

Opportunity

Australia could establish an advisory group, reporting to government, to co-design and oversee the development and implementation of enabling systems, pathways, evaluation and research to optimise access and use of RWD in HTA.

The advisory group would have:

- Representation from all stakeholder groups, including but not limited to government (including PBAC and MSAC), data stewards, commercial sector, consumer representatives (including patients, carers and families), and infrastructure, data and methodology experts (e.g., Australian Research Data Commons (ARDC), academic and other researchers). We encourage the development of terms of reference and governance arrangements that address conflicts of interest and enable a patient-centred solution.
- Transparent terms of reference, including scope, purpose, duration, workplan, resourcing, and evaluation framework.
- Links to international entities with existing RWD and RWE frameworks that can be leveraged and adapted for use across the Australian HTA lifecycle.
- Partnerships with data stewards to facilitate access to data applicable to HTA.

This advisory group would develop and implement an Australian-specific framework for the use of RWD for HTA that would:

- Provide transparent guidance for stakeholder partnerships (e.g., sponsor-researcher, sponsor-HTA body, and HTA body-researcher partnerships) and consumer engagement across all processes.
- Collaboratively determine where, when, and how RWD and RWE can be used to support HTA in Australia.
- Outline guidance for sponsors regarding the acceptability of RWE for different purposes across the HTA lifecycle.
- Identify 'high-value' RWD sources and develop standards for data quality assessment.
- Specify best-practice RWD data infrastructure and develop recommendations for RWE quality assessment including best-practice methods and reporting.
- Develop a cross-sectoral capacity building strategy that addresses education requirements, resourcing and workforce planning.

Immediate steps

In the immediate term, Australia could:

- Form the advisory group and identify representatives from all relevant stakeholders to partner in the development of an Australian-specific HTA framework.

- Draft transparent terms of reference for the advisory group, including scope, purpose, duration, workplan, resourcing, and evaluation framework.
- Establish links to international entities with existing RWD and RWE frameworks that can be leveraged and adapted for use in the Australian HTA context.
- Identify 'high-value' priority RWD sources and foster partnerships with data stewards to enable appropriate data access.
- Outline guidance for all levels of government regarding harmonisation of data governance arrangements.
- Draft process of RWD and RWE quality assessment.

Within 12 months

Within 12 months the established advisory group could:

- Finalise transparent terms of reference for the advisory group, including scope, purpose, duration, workplan, resourcing, and evaluation framework.
- Collaboratively determine where, when, and how RWD and RWE can be used to support HTA in Australia.
- Formalise partnerships with data stewards to facilitate access to data applicable to HTA.
- Outline guidance for sponsors regarding the acceptability of RWE for different purposes across the HTA lifecycle.
- Provide transparent guidance for stakeholder partnerships (e.g., sponsor-researcher, sponsor-HTA body, and HTA body-researcher partnerships) and consumer engagement across all processes.
- Develop a cross-sectoral capacity building strategy that addresses education requirements, resourcing and workforce planning.
- Finalise recommendations for best-practice RWD quality assessment framework and a RWE methods and reporting framework.

Longer-term

In the longer term, Australia could:

- Continually evaluate the Australian framework for the use of RWD for HTA, in partnership with all relevant stakeholders, making recommendations and amendments as needed.
- Implement the strategic workforce plan.

TRUST

Opportunity

Australia could develop a strategic approach to increase confidence, awareness, and acceptance of cross-jurisdictional and cross-sectoral RWD access and use in HTA. This approach should centre

consumer and community engagement and co-design, leverage and integrate existing international activities and guidelines, incorporate Australian context and evidence, and fine tune responses and messages specific to HTA. Critically, Australia should continue to develop and enhance systems that ensure privacy protections and data security.

Immediate steps

In the immediate term, Australia could:

- Socialise the benefits of using RWD for HTA with the broader Australian community (e.g., by leveraging compelling use cases).
- Establish a public register of use cases where RWE has informed HTA decisions, including expected timeframes for reporting.
- Review the data safeguards and information and communications technology (ICT) data protections for 'high-value' data collections.
- Develop a risk-based data access framework that enables secure access to RWD for trusted users.

Within 12 months

Within 12 months, Australia could:

- Increase transparency around the whole-of-data lifecycle, from collection through to evidence generation, to build confidence in the validity of RWE for HTA.
- Develop core principles that should be followed to deliver transparent RWE (such as those outlined in the NICE guidelines):
    - High quality, relevant RWD
    - Transparent reporting of study planning, conduct, and reporting
    - Best practice evidence generation methodology.

Longer-term

In the longer term, Australia could:

- Implement a learning system with an ongoing cycle of case studies demonstrating the application and utility of RWD/RWE in HTA.
- Evaluate and determine the most effective methods to communicate and build trust with the Australian public regarding use of RWD in HTA, and adapt where necessary.
- Regularly review the data safeguards and information and communications technology (ICT) data protections.
- Continuously improve and implement pathways for appropriate access to high-value RWD for relevant stakeholders (including the commercial sector).

DATA INFRASTRUCTURE

Opportunity
Australia could develop a dynamic, enduring *whole-of-government* data infrastructure, including transparent and streamlined governance, that is fit-for-purpose to accelerate RWE development for HTA. This infrastructure should evolve over time, based on the needs of HTA agencies and other stakeholders. It should also be harmonised using international standards, flexible to accommodate treatment landscape changes, scalable to incorporate emerging novel datasets and allow transparent data quality assessment. Integrated health and social data from a *single* populous jurisdiction may be fit-for-purpose to address some research questions. These data may be more rapidly accessible and offer depth across multiple sectors.
Immediate steps
In the immediate term, Australia could: • Review and consider expanding the definition of RWD (for HTA) to reflect the Australian context and evolving nature of the data landscape. • Document ethics and governance structures for priority RWD collections. • Identify core priority Australian RWD collections that are fit-for-purpose for HTA requirements. • Safely expand access to existing priority RWD collections for researchers and the commercial sector for the purposes of supporting HTA. • Set minimum recognised data quality standards and implement data validation and reporting processes for priority RWD collections. • Implement data quality assessment frameworks to ensure that priority RWD collections are accurate and reliable.
Within 12 months
Within 12 months, Australia could: • Co-develop (with relevant stakeholders) a business case for a sustainable, contemporary, accessible, enduring, high-quality, and safe data ecosystem, with user interfaces. • Harmonise data access across government departments for government-held Australian RWD collections that are fit-for-purpose for HTA. • Coordinate adoption of the FAIR (findable, accessible, interoperable, reusable) principles[4] across the HTA data ecosystem. • Develop enhanced data governance frameworks including a pathway for third party access to 'high-value' unit record RWD for HTA in an inclusive and safe way (i.e., for the commercial sector). • Plan a national RWD human resource capability pipeline. • Identify priority data curation needs to ensure data are contemporary.

- Implement RWD curation and harmonisation activities for priority RWD collections including standardisation of clinical coding and terminology that is consistent with international standards[42].
- Identify and prioritise enrichments to core Australian RWD collections that would enhance support and utility for HTA.
- Identify international data standardisation approaches (e.g., Common Data Models) that facilitate integration of disparate data both nationally and internationally (either in a unified data resource or via distributed data analytics where integration is not possible).
- Set data quality standards and implement data validation and reporting processes for all RWD collections used for HTA, including requirements for metadata on data provenance, structure and quality and minimum data validation/verification metrics.
- Develop a publicly accessible repository of data management and analytical syntax.

Longer-term

In the longer term, Australia could:

- Co-design and build an enduring sustainable, safe, high quality and fit-for-purpose data ecosystem.
- Continuously identify and fill RWD gaps for HTA.
- Conduct horizon scanning of global data developments.
- Conduct ongoing RWD curation and harmonization activities across all RWD collections.
- Conduct ongoing maintenance and updates of existing RWD to maintain relevance and fitness-for-purpose for HTA.

METHODS

Opportunity

Australia could develop a multi-stakeholder coordinated approach to transparent evidence development using best-practice methods for HTA, spanning data standardisation, standardised analytics, and reporting.

Immediate steps

In the immediate term, Australia could:

- Leverage international mechanisms for pre-registration of standardised protocols leveraging RWD (either publicly or in confidence, as appropriate).
- Leverage international standards for use of best-practice methods to analyse RWD, including methods to address bias and confounding.
- Leverage existing RWE reporting templates that include consideration of research question(s), study design, population definition, intervention, comparator, statistical

analysis approach, bias and confounding control, quantification of uncertainty, and interpretation and communication of results. • Establish a national community of practice with cross-sectoral membership.
Within 12 months
Within 12 months, Australia could: • Plan a national RWE human resource capability pipeline including identifying talent and develop training for all sectors. • Identify, prioritise and fund RWD methods research and development to align international best practice with the Australian context.
Longer-term
In the longer term, Australia could: • Continue to engage globally with other HTA agencies, subject matter experts, and methods development efforts. • Implement a national RWE human resource capability pipeline, including identifying talent and developing training for all sectors. • Support ongoing education and capability development in HTA methods to ensure currency and alignment with international standards. • Invest in methodological capacity across sectors.

Our report highlights a strategic approach to developing an enabling infrastructure which will enhance the value of RWE to support HTA in Australia. RWD is both dynamic and iterative and hence the options outlined here are designed to accommodate the rapidly evolving HTA, infrastructure, data, and methodological landscape. Prioritising efforts towards more streamlined and transparent ethics and governance processes for data access is a key foundational step in the acceleration of RWE development for HTA in Australia. Critically, we support a global perspective in Australia's approach to generating robust evidence from these data. There are an abundance of frameworks, tools and methodological approaches that can be leveraged or readily adapted to our local context which will facilitate timelier implementation. Finally, we endorse a co-ordinated, multi-stakeholder, patient-centric, collaborative approach to this effort, to ensure long-term viability and the wise use of resources and infrastructure.

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APPENDIX A: Bibliography of key resources and literature

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US regulatory

FDA Real World Evidence: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Framework for FDA's Real-World Evidence Program: https://www.fda.gov/media/120060/download

SENTINEL: https://www.sentinelinitiative.org/

OHDSI: https://www.ohdsi.org/

PCORnet: https://pcornet.org/

Europe regulatory

EMA real world evidence framework: https://www.ema.europa.eu/en/documents/report/real-world-evidence-framework-support-eu-regulatory-decision-making-report-experience-gained_en.pdf

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DARWIN-EU: https://www.darwin-eu.org/

Canada regulatory

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Health Canada RWD/RWE quality: https://www.canada.ca/en/services/health/publications/drugs-health-products/real-world-data-evidence-drug-lifecycle-report.html

CADTH RWE for decisions: https://www.cadth.ca/real-world-evidence-decision-making

CNODES: https://www.cnodes.ca/

International professional societies

ISPE RWE taskforce: https://www.pharmacoepi.org/strategic-initiatives/rwe-task-force/

ISPE RWE collaborative: https://www.pharmacoepi.org/communities/sigs/rwe-collaborative/

ISPE RWE for decisions: https://www.pharmacoepi.org/strategic-initiatives/rwe-forregulatory-decision-making/

ISPOR RWE: https://www.ispor.org/strategic-initiatives/real-world-evidence

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Monash University: https://www.monash.edu/medicine/sphpm/registries

Australian data stewards

AIHW: https://www.aihw.gov.au/our-services/data-linkage

ABS: https://www.abs.gov.au/about/data-services/data-integration/integrated-data/multi-agency-data-integration-project-madip

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APPENDIX B: Sources and types of Australian RWD

Table B.1: Key real world data sources that have been used, or could be used, for HTA in Australia

Key Australian data sources	Data steward	Linkable
ADMINISTRATIVE		
• Pharmaceutical Benefits Scheme claims, including authorities information	• DoHAC and Services Australia	✓
• Medicare Benefits Schedule claims	• DoHAC	✓
• National Hospitals Data Collection	• AIHW	✓
• Hospital separations	• State DoH	✓
• Emergency department presentations	• State DoH	✓
• National Aged Care Data clearinghouse	• AIHW	✓
• Mental health ambulatory data collections	• State DoH	✓
• Controlled drugs data collections	• State DoH	✓
REGISTRY		
• Births	• State Registrar	✓
• Deaths	• State Registrar	✓
• Causes of death	• ABS	✓
• Notifiable conditions	• State DoH	✓
• Cancers	• State DoH	✓
• Australian Cancer Database	• AIHW	✓
• Australian Immunisation Register	• DoHAC	✓
• Breast cancer screening registries	• State DoH	✓
• National Cancer Screening Register	• DoHAC	✓
• Australian and New Zealand Assisted Reproduction Database[1]	• Uni of NSW	✓
• Australian Dementia Network Registry[2, 3]	• Monash Uni	✓
• Prostate Cancer Outcomes Registry – Australia and New Zealand[2, 3]	• Monash Uni	✓
• Australian and New Zealand Myeloma and Related Diseases Registry[2, 3]	• Monash Uni	✓
• Australian and New Zealand Lymphoma and Related Diseases Registry[2, 3]	• Monash Uni	✓
• Australasian Interstitial Lung Disease Registry[4]	• Uni of Sydney	✓
• Australian Leukodystrophy and White Matter Disorders Registry[5]	• Australian Genomics	✓
SURVEYS (SELF-REPORT)		
• Australian Census of Population and Housing (Census)	• ABS	✓
• National Health Survey	• ABS	✓
• Survey of Disability, Ageing and Carers (SDAC)	• ABS	✓
• Australian Early Development Census (AEDC)	• Dept of Education	✓

ELECTRONIC HEALTH RECORDS		
• LUMOS primary care data	• NSW Health	✓
• MedicineInsight primary care data	• ACSQHC	✓
• PATRON primary care data[6, 7]	• Uni of Melbourne	✓
• Aurora primary care data[8]	• Outcome Health	✓
• Hospital-based information systems	• State DoH	✓
• My Health Record	• AIHW/DoHAC	✓
MOLECULAR		
• Mitochondrial disorders WES and WGS data[9]	• Australian Genomics	✓
• Neuromuscular diseases WGS and RNASeq[9]	• Australian Genomics	✓
• ASPREE Genomics program[10]	• Monash Uni	✓
• Medical Genome Reference Bank[11, 12]	• Garvan Institute	✓
CASE REPORT		
• Database of Adverse Event Notifications (DAEN)	• TGA	✗

Abbreviations: DoHAC – Commonwealth Department of Health and Aged Care; AIHW – Australian Institute of Health and Welfare; DoH – Department of Health; ABS – Australian Bureau of Statistics; ACSQHC – Australian Commission for Safety & Quality in Health Care; WES – whole-exome sequencing; WGS – whole-genome sequencing; RNASeq – RNA sequencing; TGA – Therapeutic Goods Administration.

Key: ✓ =can be linked; ✓ = can possibly be linked; ✗ =cannot be linked

Table B.2: Linked real world data sources with potential for use in HTA in Australia

Key Australian linked data sources	Custodian
PROSPECTIVE COHORT STUDIES	
• 45 and Up Study • Australian Longitudinal Study of Women's Health	• Sax Institute • Newcastle and QLD Unis
CLINICAL QUALITY REGISTRIES	
• Australian Stroke Clinical Registry	• The Florey, the Stroke Foundation & SSA
POPULATION-WIDE LINKAGES OF HEALTH AND SOCIAL DATA	
• Person Level Integrated Data Asset (PLIDA; formerly Multi-Agency Data Integration Project, MADIP): Enduring linkage of health, education, income, taxation, employment • National Integrated Health Services Information (NIHSI) asset[13] and future National Health Data Hub: Enduring linkage of health data and some population indicators • COVID Register and linked data set[14]	• ABS • AIHW • AIHW

Abbreviations: SSA – Stroke Society of Australasia; ABS – Australian Bureau of Statistics; AIHW – Australian Institute of Health and Welfare

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APPENDIX C: Barriers and enablers of access to RWD for HTA in Australia

Table C.1: Legal barriers and enablers to RWD availability for HTA in Australia

Barriers	Proposed / potential enablers
Inconsistent and conflicting data sharing legislation within public sector (Commonwealth and State and Territory) and between public and private sectors Some datasets cannot be legally shared	• Simplified and harmonised legislation centred on the national interest • Further legislation to enable two-way sharing of cross-sectoral data between jurisdictions (for example, modifications to the DAT Act, ABS Act, AIHW Act, and WA legislation) • Legal frameworks specific to RWD and the generation of RWE
The 2023 Intergovernmental Agreement on data sharing between Commonwealth and State and Territory governments does not mention research	• Intergovernmental agreement that explicitly includes research and also cross-sectoral access and use for RWE generation for HTA
The AIHW NIHSI/NHDH approved research purposes *exclude* evidence generation to support regulation of health technologies	• Approved purposes for NIHSI/NHDH that explicitly include RWE generation for HTA
Consent arrangements for some datasets prevent on-sharing (e.g., private sector datasets)	• Co-designed dedicated guidance and processes for obtaining consent including opt-out consent

Abbreviations: DAT – Data Availability and Transparency; ABS – Australian Bureau of Statistics; AIHW – Australian Institute of Health and Welfare; NIHSI – National Integrated Health Services Information; NHDH – National Health Data Hub; WA – Western Australia.

Table C.2: Socio-cultural barriers and enablers to RWD availability for HTA in Australia

Barriers	Proposed/potential enablers
Societal privacy concerns and distrust in data protections	• Communication strategy about the RWD opportunities, risks, and safeguards • Co-designed information about RWD protections, the RWD governance frameworks, and the ethical framework including the role and independence of ethics committees • Comprehensive and regular Privacy Impact Assessments (PIAs) of Australian RWD infrastructure and the RWE generation system • Co-designed evaluation framework for RWD and RWE in Australia, including data protection regulation and data governance frameworks • Co-designed Equity Principles for the access and use of RWD in Australia • An Australian RWD workforce plan that promotes diversity, and inclusivity
Societal expectation of informed consent for data sharing and reuse	• Compelling use cases and public benefit impact stories to strengthen and maintain public trust in RWD and RWE generation • Nationally agreed opt-out consent framework; accessible information about the circumstances under which people can opt out from having their data shared • Co-designed information about the need for RWD to incorporate emerging and new data sources (e.g., genomic data and other biomarkers) to improve outcomes for people with rare diseases, and the impacts of opting out • Research to understand public perspectives about RWD/RWE and how people make decisions regarding consent for data sharing for RWE
HTA stakeholder non-acceptance of RWE	• An overarching cross-sectoral RWD/RWE partnership advisory body and coordinated cross-sectoral working groups • Respectful collaboration and open communication across sectors • Documented criteria for acceptable/unacceptable RWD quality • Documented stakeholder concerns about using RWE for HTA • Documented real world scenarios of high unmet medical need where HTA would benefit from RWD • Documented examples of the "efficacy-effectiveness gap"[1] (the difference between the outcomes of RCTs and those observed in real world clinical practice)

Table C.3: Data steward barriers and enablers to RWD availability for HTA in Australia

Barriers	Proposed/potential enablers
Uncertainty about consent requirements for data sharing	• Co-designed guidance regarding the legal and ethical frameworks for disclosing and reusing personal information for RWD research
Data privacy and security concerns	• Co-designed cross-sectoral guidance and education materials about data safeguards and ICT protections (e.g., Five Safes Framework[2, 3], secure remote access environments) • Enhanced use of national data linkage keys or another unique person-level identifier to reduce the transfer of personally identifying information
Perceived lack of control over who can access the data and how they can use it	• Co-designed governance arrangements • Co-designed cross-sectoral data sharing agreement templates
Low trust in some data users	• An overarching cross-sectoral RWD/RWE partnership advisory body and coordinated cross-sectoral working groups • Co-designed governance arrangements • Adoption of international standards for the conduct of RWE studies, including transparent pre-specified research processes, use of structured templates, and registered protocols • Routinely reviewed and enhanced data protections within secure remote access environments, keeping pace with international ICT developments
Constrained or no resources to extract and curate the data and manage queries	• A federated data infrastructure where data linkage units can act on behalf of data stewards
Excessive costs of ad hoc data linkage	• A cost sharing approach agreed by all stakeholders including the commercial sector, with incentives to integrate high-value, high-quality RWD in enduring data assets
Inadequate benefits or incentives to share data (e.g., private health care providers)	• An overarching cross-sectoral RWD/RWE partnership advisory body and coordinated cross-sectoral working groups • A co-designed HTA system that preserves patient privacy, maximises the potential for public benefit, protects commercial-in-confidence material, and generates benefit for data owners

Abbreviations: ICT – Information and communications technology

Table C.4: Operational and technical barriers and enablers to RWD availability for HTA in Australia

Barriers	Proposed/potential enablers
Lack of awareness of RWD	• Discover and prioritise RWD of significance to HTA • Identify and address any legal barriers to RWD inclusion in HTA data infrastructure • Identify and prioritise RWD gaps • Coordinated adoption of the FAIR (findable, accessible, interoperable, reusable) principles[4] across the HTA data infrastructure
High costs associated with collecting, checking, and curating high quality RWD	• A cost sharing approach agreed by all stakeholders including the commercial sector • Investment in data infrastructure ICT & human resources
Excessive time taken to curate some RWD of significance to HTA	• Prioritise, interrogate, resource and improve the vital RWD pipelines and workflows • Regularly re-link datasets in enduring linked data assets
Lack of RWD interoperability	• A cross-jurisdictional and cross-sectoral data strategy that drives and rewards data interoperability and automation
Incomplete personal identifiers (e.g., name code) on some RWD collections hinders accurate and efficient linkage	• Guidance and standard operating procedures for data processing, linkage methodology, and reporting of linkage statistics • Validation studies to understand and quantify linkage accuracy and potential biases
Non-standardised RWD elements; data of poor or unknown quality	• Adoption of Australian metadata standards (e.g., METeOR) at the point of data collection • Identify gold standard data sources and conduct validation studies
Highly complex and large RWD	• A federated data infrastructure where data linkage units can act on behalf of data stewards and curate data
Data integration is reliant on probabilistic data linkage, which is slow and inaccurate	• Use of Individual Healthcare Identifier (IHI) or another unique person-level identifier at data collection • A pathway for deterministic or hybrid probabilistic data linkage • Ongoing implementation of national linkage keys

Abbreviations: ICT – Information and communications technology; METeOR – AIHW Metadata Online Registry

Table C.5: Barriers and enablers to RWD access for HTA in Australia

Barriers	Proposed/potential enablers
Duplicative, burdensome governance requirements	• An overarching cross-sectoral RWD/RWE partnership advisory body and coordinated cross-sectoral working groups • Unified, streamlined, and transparent governance framework supported by a fully digitised application and approval process for access to all relevant RWD for HTA (cross-jurisdictional and cross-sectoral) • Published approval timelines and routine evaluation against agreed indicators
Excessive cost and time taken to negotiate data sharing agreements	• Resourced and distinct capabilities to support timely and cost-effective cross-sectoral RWD access • Co-designed cross-sectoral data sharing agreement templates
Duplicative, burdensome HREC reviews	• As per PLIDA/MADIP and NIHSI, proposal review and approval by a single accredited HREC under the National Mutual Acceptance (NMA) scheme • To sustain and maintain trust, the HREC must have recognised expertise in the assessment of RWD research • A system that supports HREC review and approval of *programs* of RWD research, to reduce the number of applications and costs for related projects by the same team
Inadequate First Nations control over access and use of data about First Nations people	• Coordinated adoption of the CARE (collective benefit, authority to control, responsibility and ethics) principles[5] for Indigenous Data Governance • First Nations-designed and implemented Indigenous Data Governance pathway for RWD research about First Nations people • First Nations-designed and implemented HREC pathway for RWD research about First Nations people • First Nations-led identification of First Nations people in linked datasets
Excessive data access costs for non-government researchers	• A cost sharing approach agreed by all stakeholders including the commercial sector
Inequitable support for researchers based in different sectors	• Resourced and distinct capabilities to support timely and cost-effective cross-sectoral RWD access

Abbreviations: PLIDA – person-level integrated data asset; MADIP – multi-agency data integration project; NIHSI – National Integrated Health Services Information data asset; HREC – human research ethics committee

Table C.6: Commercial sector barriers and enablers to RWD use for HTA in Australia

Barriers	Proposed/potential enablers
HTA stakeholder evidentiary needs are uncertain	• An overarching cross-sectoral RWD/RWE partnership advisory body and coordinated cross-sectoral working groups • Documented Australian regulator and payer RWE requirements and openness
Lack of sponsor guidance on how to apply and weigh RWE in regulatory submissions	• Regulatory guidance, including a strategy for addressing evidence gaps • HTA processes that allow for early consultation with regulators on the acceptability of RWE for both pre- and post-market submissions
Lack of access to end-to-end RWD infrastructure and capability	• Cross-sectoral collaboration and alignment of interests • Investment in cross-sectoral infrastructure and capability • Partnerships to bring emerging and new types of RWD into collective RWD infrastructure • Access to fit-for-purpose RWD, including national, representative datasets, and highly curated datasets
Uncertainty regarding Australian RWD strategy	• An overarching cross-sectoral RWD/RWE partnership advisory body and coordinated cross-sectoral working groups
Risk of disclosing sponsors' commercially sensitive information	• Co-design processes that serve to protect commercial-in-confidence material whilst retaining methodological transparency

Table C.7: Data barriers and enablers to RWD use for HTA in Australia

Barriers	Proposed/potential enablers
Inadequate information and uncertainty about RWD quality, representativeness, and utility	• High-quality open access metadata for all datasets • Synthetic data for vital RWD to build capacity and enable methods development • A cross-sectoral working group with a remit to (i) identify uncertainty in RWD/RWE and strategies to reduce it, and (ii) prioritise asset-wide research to assess data quality and representativeness • Research to optimize the quality of data identifying disadvantaged populations • Feedback to RWD stewards regarding data quality, and supported quality improvement programs
Inadequate RWD standardisation	• Adoption of Australian metadata standards (e.g., METeOR) at the point of data collection • Harmonised, contemporary state and territory hospital datasets • Distributed or centralised RWD infrastructure that supports high-quality data curation • Application of an international CDM to datasets of significance to HTA (e.g., OHDSI)
Lack of interoperability between data sources, especially EHRs	• Research to standardise the coding of clinical concepts • System architecture that considers and optimises all relevant data pipelines
Gaps in RWD that limit the quality of the RWE (e.g., private prescriptions; prescribed drug dosages; treatment complications managed in community; precise disease phenotype (clinical/genomic/biomarker data); and disease progression)	• Cross-sectoral prioritisation of high-quality, high-value existing RWD that is not yet available for research • A pathway to fast-track integration of existing RWD • National enhanced data collection for high-cost, high-burden, and ultra-rare diseases that cannot be identified in current data collections, e.g., TNM stage, tumour biomarkers for selected cancers • Investigate validity of proxies for disease progression in administrative datasets

Abbreviations: METeOR – AIHW Metadata Online Registry; CDM – Common Data Model; ODHSI – Observational Health Data Sciences and Informatics

Table C.8: Organisational barriers and enablers to RWD use for HTA in Australia

Barriers	Proposed/potential enablers
Uncertainty in robustness of RWE Inadequate methodological transparency and RWE reproducibility The use of inappropriate statistical methods	• A national RWD human resource capability pipeline • Communities of practice with cross-sectoral membership • Cross-sectoral RWE methods development and evaluation of emerging study designs • End-to-end transparency of RWD research • Pre-registration of study designs and statistical analysis plans, and use of international structured templates • Adoption of existing, fit-for-purpose reporting framework to support assessment of RWD study quality (e.g., STROBE) • Application of an international Common Data Model (CDM) to RWD of significance to HTA • Application of a recognised framework for cohort construction and analyses (e.g., OHDSI) • Sharing of syntax used for data transformation, cohort creation, and analytic results generation
Excessive costs	• Resourcing distinct capabilities that support cross-sectoral RWD use including vetting of aggregate statistical outputs • Reasonable cost recovery models for use of secure remote environments • A negotiated agreement with statistical software providers (e.g., SAS) to allow non-government researchers to bring their institutional licenses into secure remote environments
Potential for unintended harm, disrespect or injustice to communities represented in the data	• Co-designed Equity Principles for the use of RWD • Integration of social data to enable adjustment by the social determinants of health • Research to investigate and make recommendations for improving the representativeness of RWD • Empowerment and self-determination of subpopulations across the RWD ecosystem • Workforce training in the cultural sensitivities in RWD collection, use, analysis, interpretation and reporting • Australian RWD workforce plan that promotes diversity and inclusivity
Lack of agreed indicators for underserved or priority populations	• Communities of practice with cross-sectoral membership • Co-designed algorithms to derive indicators • Systematic research to identify whether there are biases that inequitably impact subpopulations in the source RWD collections or because of probabilistic linkage

Barriers	Proposed/potential enablers
Non-timely identification of research required to inform HTA regulatory decisions	• An overarching cross-sectoral RWD/RWE partnership advisory body with coordinated cross-sectoral working groups and a mechanism to prioritise research
Inadequate capacity in RWD skills	• An Australian RWD workforce plan that promotes diversity, inclusivity, growth, retention (job security), and career progression

Abbreviations: STROBE – Strengthening the Reporting of Observational Studies in Epidemiology guidelines; CDM – Common Data Model; ODHSI – Observational Health Data Sciences and Informatics

Appendix C References

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