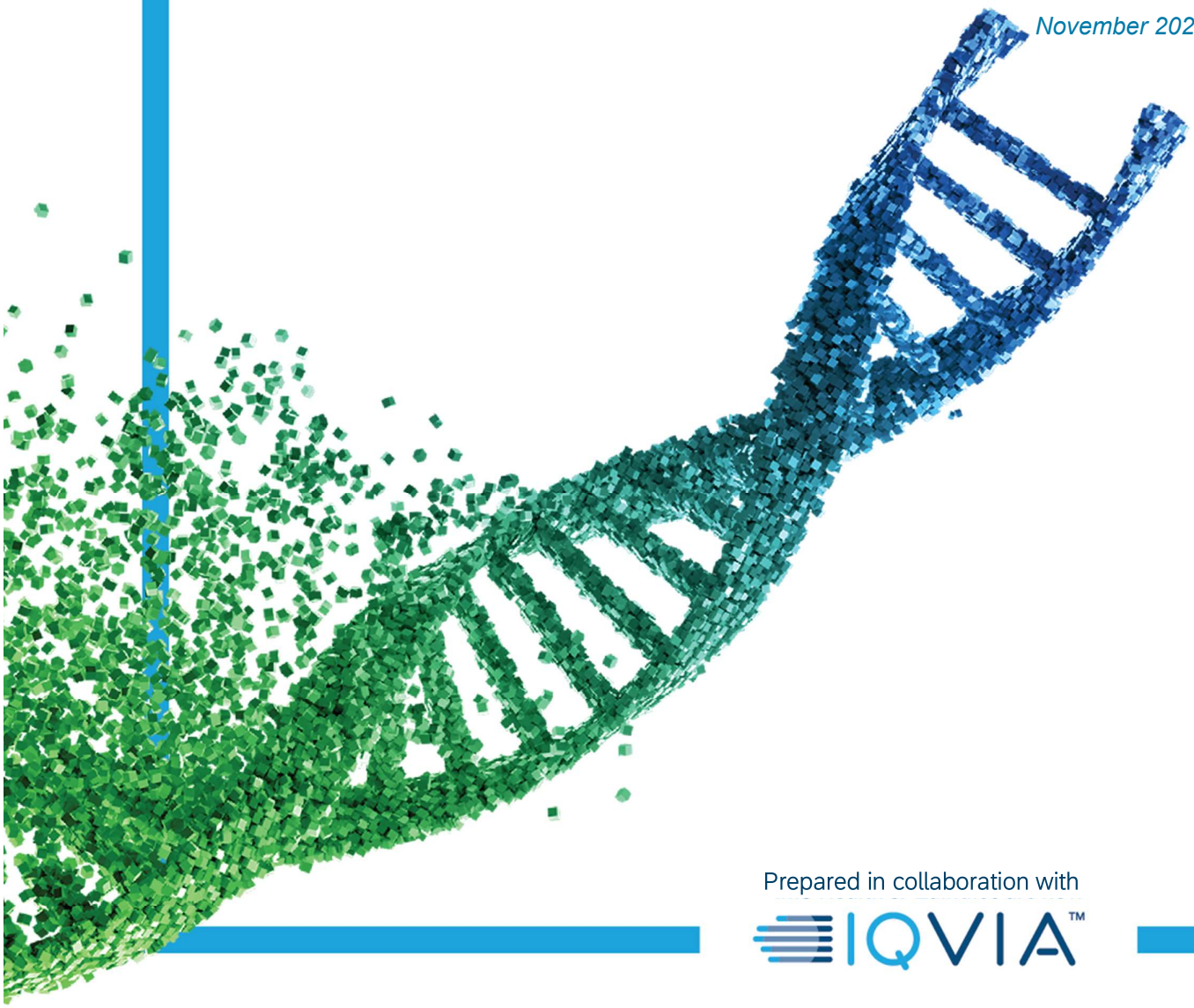
Medicines Australia

THE EVOLVING ROLE OF REAL-WORLD EVIDENCE IN AUSTRALIA

Report Prepared by the Oncology Industry Taskforce RWE Working Group, a Medicines Australia Initiative

November 2020



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WHAT IS REAL WORLD EVIDENCE (RWE)?

Real-world evidence (RWE) is a concept that has been long-present in healthcare industry; research leveraging observational registries and claims databases has been commonplace for several years. However, the concept has gained considerable momentum within the last decade, as technology has facilitated exponential growth in real world data (RWD) generation, and as payer and regulator needs have evolved.

Figure 1 shows the evolution in the number of health technology assessment (HTA) submissions leveraging RWE from 2012 to 2019. This analysis shows that the proportion of submissions leveraging RWE has doubled from 2012 to 2019. This period also coincides with growing use of RWE to support regulatory submissions – with both the EMA and FDA recently publishing official guidance on use of RWE for regulatory purposes.

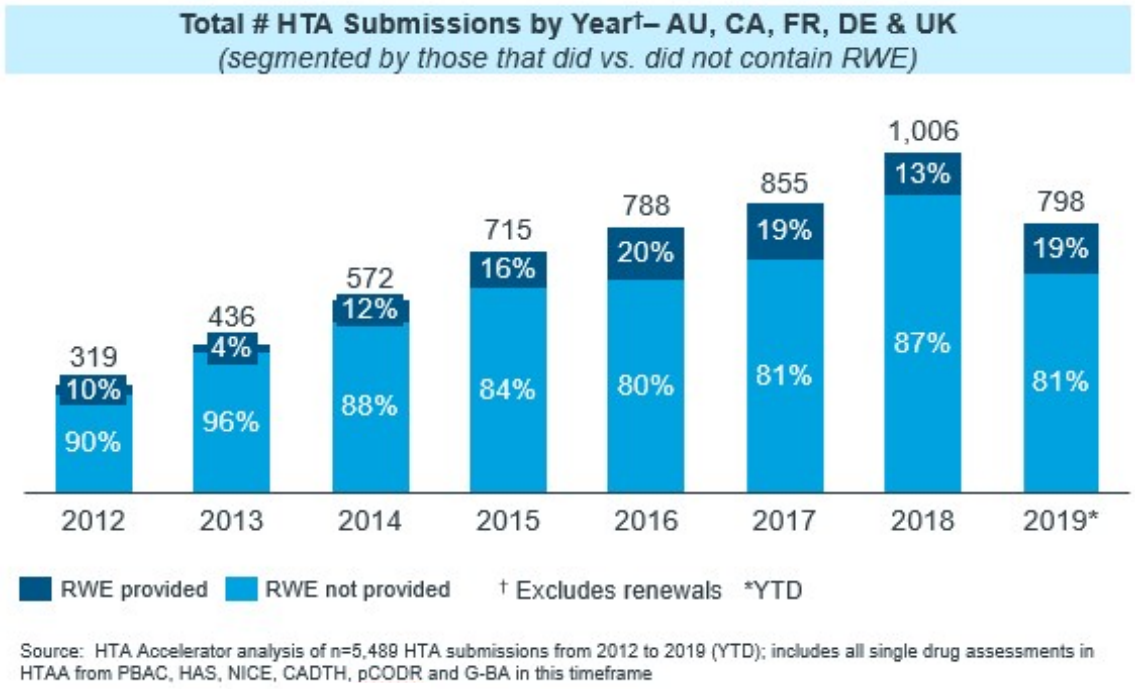

Figure 1 Growth of Real-World Evidence (RWE) Over Years
Source: IQVIA HTA Accelerator

A study on the consensus definition of RWD/E[1] (or lack thereof) uncovered a high degree of disparity in definitions adopted by various stakeholders. Some stakeholders defined any data collected outside the context of the randomized clinical trial (RCT) as being RWE – a definition which, for example, would include pragmatic clinical trials (PCT). Other approaches limit the definition of RWE to non-interventional data only, or even more narrowly to only data collected in a non-experimental setting (e.g., electronic medical record or administrative / claims data).

Moreover, a broad range of "traditional" and "emerging" data sources can be classified as Real-World Data. Figure 2 depicts a spectrum of some of the most common RWD sources, ranging from "traditional" retrospective data on the left, to more "traditional" prospective data on the right – with "emerging" data sources increasingly used for RWE generation purposes (such as genomics and mHealth data) in the centre.

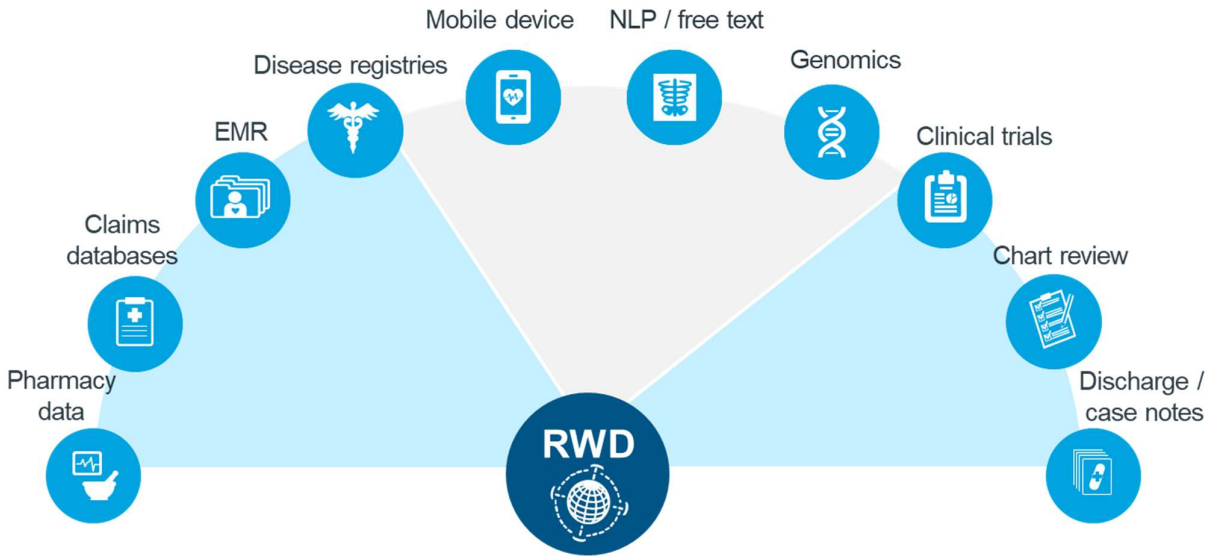

Figure 2 Sources of Real-World Data

NLP = Natural Language Processing

For the purpose of this report, in order to account for a wide range of current and potential future applications of RWD/E, the remainder of the views set out in this paper consider a broad definition in line with the US Food and Drug Administration (FDA) definition of RWD/E, i.e. "healthcare information derived from multiple sources outside of typical clinical research

[1] What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews, Makady et al 2017

settings, including electronic medical records (EMRs), claims and billing data, product and disease registries, and data gathered by personal devices and health applications”[2].

[2] U.S. Food and Drug Administration, “Use of real-world evidence to support regulatory decision-making for medical devices,” August 31, 2017, fda.gov.

AN INDUSTRY PERSPECTIVE

The OIT RWE Members believe that stakeholder alignment and investment of time and resources is required to enable a consistent approach to evidence planning and generation of RWD. Further, while these are matters of importance within oncology, OIT RWE Members acknowledge broader application beyond this therapy area.

Importantly, rather than competing with existing more traditional forms of evidence, OIT RWE Working Group Members believe RWE provides opportunities to augment the evidence base and provide additional value by providing a more complete picture of treatment effectiveness and safety within the real-world setting.

Members consider key challenges as;

- Differing views amongst stakeholders on the value of RWE
- Perceptions of RWE being ranked low in terms of adding value to the evidence base
- Planning that is often too late in terms of meeting the needs of key industry functions, e.g. regulatory, market access, commercial teams.
- Infrastructure and resource allocations supporting collection of RWD and delivery of RWE

Members acknowledge how RWE has been playing a bigger part in the value assessment within the evolving ecosystem of other countries. Further, Members believe that, with an integrated healthcare system and largely universal access, opportunities exist within Australia to take a leadership position with RWD through evidence generated to educate and inform on the appropriate investments in existing and newly available medicines.

However, the realisation of these opportunities will require significant work and collaboration across the healthcare sector, between industry, government, and other stakeholders.

DELIVERING CROSS-STAKEHOLDER VALUE THROUGH RWE

Real-World Evidence offers benefits regarding its generalisability, strong external validity, and ability to address evidence gaps where RCTs are impracticable. However, the opportunities and potential solutions offered by RWE are being tempered by perceived skepticism towards RWE, an underappreciation of its value and the privileging of RCTs above other forms of evidence. The latter may, at least in part, be due to a lack of consensus amongst stakeholders on what constitutes as robust and scientific methodology for the construction and evaluation of RWE. Potential divergence between evidence generated from RCTs and RWD (e.g. the efficacy vs effectiveness gap) can lead to apprehension to invest in RWE activities amongst some stakeholders and behaviors that default toward more traditional forms of evidence amongst others when forms are presented for evaluation.

However, the advent of increasingly sophisticated analytic techniques together with increasing breadth, depth and quality of data means that RWE has the potential to play a more central role in the evaluation of health technologies and their impact within the health care ecosystem.

When generated via fit-for-purpose data, appropriate methodologies and transparent processes, RWE can add relevant and useful information that supports/enables more informed evidence-based decision-making across all stakeholder types. This includes regulators and payers, industry, physicians and ultimately, and most importantly, patients.

For payers and regulators, RWE represents a means of obtaining a more complete picture of treatment effectiveness and safety in the real-world. Indeed, findings support the value of RWE to complement clinical trials in providing a more complete view on the effectiveness and safety of treatments.[3] In addition, an ability to deliver high quality evidence appears to be possible when facilitated by clear frameworks that detail the data elements, characteristics, and the internal validation processes used.[4]

While RWE is unlikely to replace RCT-generated evidence where the latter is available, its role in the triangulation of difficult to deliver clinical outcomes, e.g. overall survival, may be relevant and important both in supporting ethical study design and overcoming such design limitations of RCTs. This is particularly relevant within the context of a healthcare industry focused on developing ‘innovative’ treatments involving drugs targeting increasingly niched target populations with high unmet medical needs, and where Phase 2 single arm studies are becoming increasingly common in HTA submissions[5].

[3] Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence, Bartlett et al 2019
[4] Friends of Cancer Research, Establishing a Framework to Evaluate Real-World Endpoints
[5] IQVIA HTA Accelerator analysis found that number of single-arm submissions globally increased from 8 in 2011 to 81 in 2018

Beyond this specific application, RWE can also help to build a more comprehensive picture of real-world populations and treatment use, allowing payers and regulators to understand therapy effectiveness and safety in larger pool of patients, for a longer period of time, in the context of real-world clinical practice. The relevant benefit for industry is complementary – enabling more comprehensive articulation of the full range of clinical, economic and humanistic benefits offered by a treatment, to be used to inform health economic and access decision-making.

RWE can also benefit the clinical community, enabling more informed decision making at the individual patient level. Because of the ability to generate RWD at scale, it can be used to support robust analysis of real-world subpopulations of interest, and to understand treatment outcomes for patients that may typically be excluded from RCTs. More generally, this means that physicians are better able to tailor treatment decisions to the individual patient. Notably, evidence already exists of this happening in practice – for example through the integration of clinical decision support tools at the point of care.

Critically, all of these potential benefits of RWE across the healthcare system ultimately converge on the underlying and unifying benefit of improved patient outcomes, driven by access to a broader range of therapies and a sharpened understanding of the "right drug for the right patient."

The remainder of this report focuses on the use of RWE in the payer setting; however, the potential role of RWE from an Access and HTA-decision-making perspective should be considered in the context of its broader role in creating shared value across the healthcare continuum. Through use of RWE, multiple stakeholders can collaboratively create, analyze and share results for better individual and population health outcomes[6].

[6] From PI to Payer to Patient: RWE From the Perspective of Each Key Stakeholder, John Doyle. http://www.pharmexec.com/pi-payer-patient-rwe-perspective-each-key-stakeholder

TRENDS IN THE USE OF REAL-WORLD EVIDENCE, IN AUSTRALIA AND BEYOND

It is important to acknowledge that RWE already has an established role as an input to HTA decision-making process in Australia. It has been used in support of a variety of use cases across the PBAC process – from "traditional" use cases such as treatment pattern analysis and estimates of financial impact using PBS data, to more "innovative" use cases such as the decisions to reimburse Blincyto and Bavencio based on single-arm studies with external Real World comparator data. Moreover, it is worth noting that PBAC guidelines do currently offer guidance on both methodological issues surrounding nonrandomized studies[7] and sources of RWD for estimating utilisation[8].

Accordingly, the current report does not take the position that RWE is not being used in the Australian HTA process, but rather suggests that it is not currently being used to its full potential – especially considering emerging methodologies and data sources that are increasingly making the generation of RWD faster and more cost-effective.

More specifically, this report serves as a call to action for stakeholders across the Australian healthcare ecosystem to engage in proactive discussion around how to pragmatically address the evidence needs of the future – in recognition of the fact that many emerging innovative therapies will require innovative approaches to evidence generation – potentially leveraging RWE as a tool to address anticipated evidence gaps. The need for a forward-looking solution will only become more pressing as advances such as genomic sequencing uncover greater numbers of rare tumour variants[9], resulting in smaller subpopulations where the traditional burden of evidence is impracticable.

In terms of how use of RWE in Australia compares with other major HTA markets, given the heterogeneity in healthcare systems across the world, it is difficult to make direct "like-for-like" comparisons. Accordingly, IQVIA has combined a quantitative analysis of information available in public summary documents (PSDs), with a qualitative assessment of information available in guidelines and the literature, to provide a holistic assessment of how approaches and attitudes differ in Australia vs. other major HTA markets (UK, France, Germany and Canada).

Analysis of IQVIA's HTA Accelerator database shows that the UK and France are clear leaders in terms of number of public summary documents referencing RWE (55% and 47% of all submissions), whereas Germany, Canada and Australia show much more limited use *as identified through PSDs*, with 10%, 6% and 5% referencing RWE, respectively. Whilst this

[7] https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf
[8] http://www.pbs.gov.au/info/industry/useful-resources/sources
[9] Real-world Data for Clinical Evidence Generation in Oncology, Khozin et 2017

may reflect a more established and familiar vocabulary for discussing RWE in PSDs in France and UK – it likely also reflects systemic and attitudinal differences driving greater use of RWE in the HTA process in these markets.

In the UK, the managed access Cancer Drug Fund allows for interim access with ongoing data collection – facilitating systematic generation of RWE to support effectiveness and safety claims in a way that is not currently possible in many other markets. Likewise, in France, a mandatory five-year resubmission requirement creates a need for post-marketing evidence on effectiveness and safety, accounting for a total of 640 instances of RWE use.

Furthermore, analysis of guidelines and statements from payers in each of these countries shows some common ground – where RCT data is available, it is almost universally preferred over RWE to demonstrate efficacy / treatment effects.

However, review of the guidelines also shows deeper, philosophical differences in attitudes to RWE; the UK, France and Canada show a far greater degree of openness to RWE – acknowledging that all forms of data are accepted provided the biases and limitations are adequately recognised. In fact, the Canadian guidelines go so far as to say that in some instances RWE is preferred to RCT data. Conversely, the PBAC and IQWiG guidelines only allow for RWE use in support of effectiveness-based claims in a very narrow set of exceptional circumstances (i.e., where RCT data is not available).

Whilst this may seem like a distinction without a difference, in practice we see that some HTA bodies carefully weigh both the internal and external validity of evidence, whereas others clearly prioritise the internal validity offered by clinical trials. In the former conception, each real-world study can be judged according to its own merit, and if found methodologically sound, could “move the needle”. In the latter, RWE is more commonly dismissed due to an over-emphasis of the “hierarchy” of evidence.

As the industry moves to a world where RCT data is becoming more ethically and logistically challenging to collect (i.e., due to increasingly targeted populations), and where feasibility and ease of RWE generation is growing, failure to collaboratively develop a pragmatic, future-fit approach to evidence generation could have profound implications for patient access to therapy.

It is important to note that RWE is not the only possible lever to facilitate access to therapies in this context. For example, in Germany, orphan drugs are automatically granted “added benefit” rating (and therefore market access) in recognition of the fact that the traditional burden of evidence is impracticable. However, this report contends that, in the Australian context, RWE represents an underutilised and potentially “quick win” lever to reduce and mitigate payer uncertainty surrounding novel oncologics, whilst ensuring timely access for high unmet need populations.

MAXIMISING THE VALUE OF REAL-WORLD EVIDENCE IN AUSTRALIA

Whilst this report acknowledges needs for broader conversations with data custodians to address some of the data access and exogenous issues, the current discussion focuses on the opportunities related to the HTA process itself, in an attempt to build toward actionable next steps.

The report contends two key challenges exist with generation and provision of RWE as part of the HTA process:

- **Methodological challenges** – where the absence of agreed frameworks, method and standards has impeded advancement in the delivery of fit-for -purpose RWE; and

- **Procedural challenges** – where opportunities may exist for pre-submission processes that assist in the planning of RWE. An extension of this may be consideration of what pre- and post-reimbursement processes might support early access in areas of high unmet medical need, in ways supported by non-RCT data collection and RWE generation that also support alignment between value and price.

With this, the remainder of this report details key recommended actions to assist each of these challenges in turn.

The first recommendation is that a stakeholder taskforce including industry, HTA, medical and evidence experts be brought together to share views on opportunities to develop frameworks and potential guidance on where and how RWE might best support the HTA process.

As a minimum, this will raise awareness amongst these key stakeholders of each other's needs, challenges, and concerns. While more ambitious, those preparing this report are optimistic that alignment on potential expansion on existing guidelines relating to the use of nonrandomized studies, potentially with future provision of more comprehensive guidelines on where RWE may and may not be appropriate, together with what methodological principles may or may not be appropriate in its generation and assessment.

It is believed that a clear framework on the generation, provision and assessment of RWE would help mitigate the causality dilemma described above – whereby the PBAC (and other payers) remain cautious of RWE due to concerns around its methodological soundness and transparency, and where pharmaceutical companies do not invest sufficiently in generating high quality, fit-for-purpose RWE due to concerns over the low likelihood of its future acceptance.

Importantly, the development of guidance on use of RWE must not seek to reinvent the wheel, but rather build upon the existing efforts of numerous other stakeholders[10] such as the GRACE checklist[11] and the ISPOR Real-World Evidence Transparency Initiative[12]. That said, the PBAC guidance herein suggested must also avoid blindly accepting recommendations and approaches from other working groups, which may not be appropriate for the Australian context.

The second recommendation concerns procedural challenges in RWE generation. Considering the current limitations to Australia's RWD ecosystem, and acknowledging that pharmaceutical companies do invest in early access initiatives it is worth considering what could be done to leverage the opportunities for data collection and analysis to support timely delivery of informative RWE in the support of tangible, near-term benefits.

However, a successful Early Evidence Generation solution will require careful design. Any such program must facilitate collection of accurate, structured data on a consistent basis, and ensure that this data can be appropriately accessed following a rigorous yet pragmatic ethics process. Potential lessons from other markets which have implemented similar programs, such as the Early Access to Medicines Scheme in the UK, should be further explored as part of this workstream.

[10] These efforts complement existing initiatives on behalf of organizations such as ISPOR and the FDA
[11] The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness, Dryer et al 2016
[12] More broadly there has been a proliferation of documents / frameworks for generation of RWE. RWE Framework: An Interactive Visual Tool to Support a Real-World Evidence Study Design, Xia et al and Data linkage in pharmacoepidemiology: A call for rigorous evaluation and reporting, Pratt et al are two examples from November 2019 alone.

CALL TO ACTION

To summarise, the report writers would like to propose the following call to action to continue the dialogue and kick-start the process of solution co-creation:

1. Organise a cross-stakeholder roundtable (including PBAC, data custodians and other informed experts) to gain alignment on the current challenges and to propose potential solution concepts;

2. Pending outcomes of #1, *form dedicated working groups focused on driving the necessary changes that enable quality RWE generation opportunities*