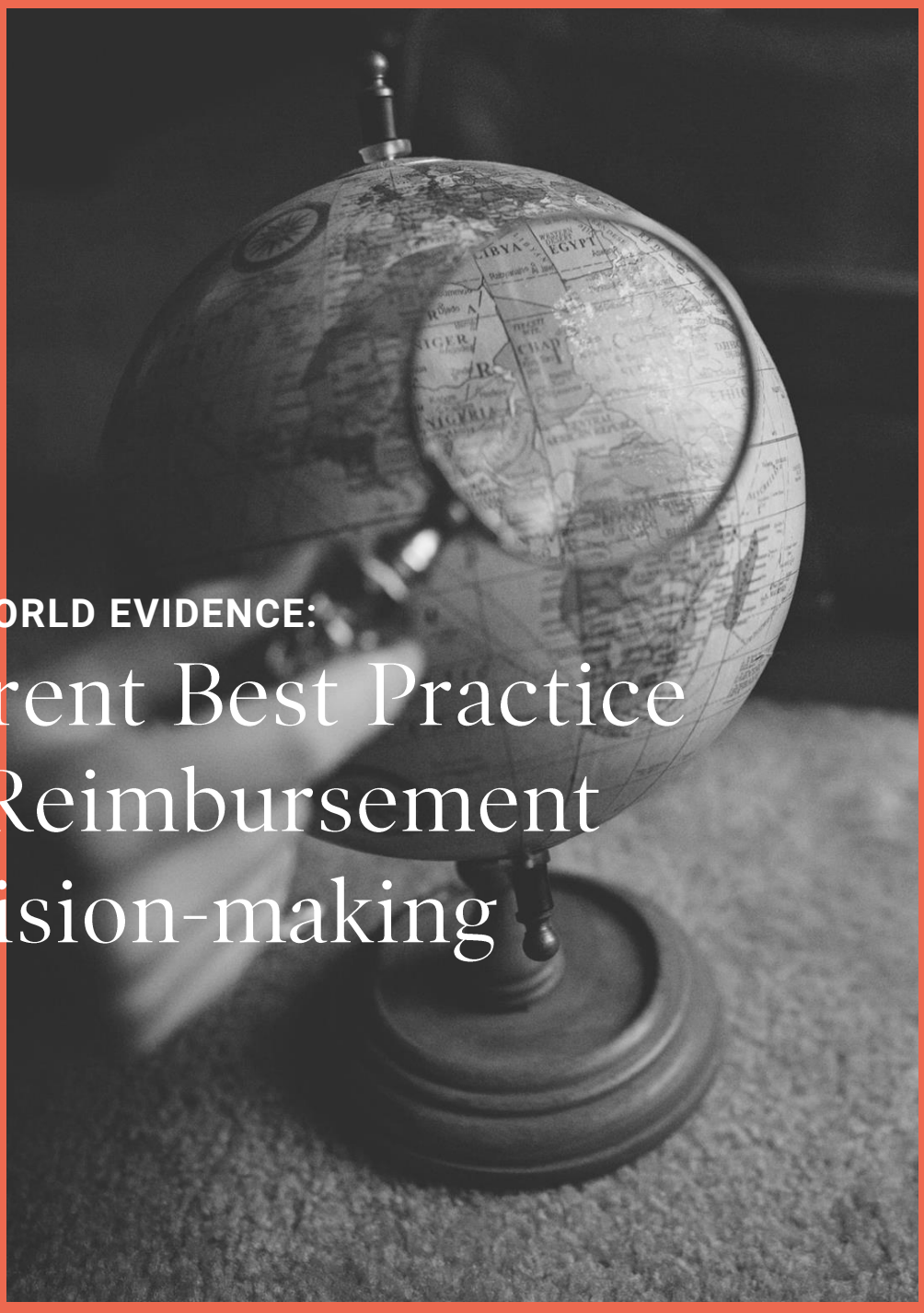
OHE



CONTRACT RESEARCH REPORT
MAY 2023

REAL-WORLD EVIDENCE:

Current Best Practice for Reimbursement Decision-making

Sian Besley
Amanda Cole
Roah-Fang Pwu
Jason Chia-Hsun Hsieh

ohe.org

OFFICE OF HEALTH ECONOMICS
CONTRACT RESEARCH

MAY 2023

REAL-WORLD EVIDENCE:

Current Best Practice for Reimbursement Decision-Making

Sian Besley
Office of Health Economics, London, UK

Amanda Cole
Office of Health Economics, London, UK

Raoh-Fang Pwu
Fu Jen Catholic University, New Taipei City, Taiwan

Jason Chia-Hsun Hsieh
New Taipei Municipal Tucheng Hospital, Chang Gung Memorial Hospital at Linkou and Chang Gung University, Taoyuan, Taiwan

---

Please cite this report as:
Besley, S., Cole, A., Pwu, R., Hsieh, C., 2023. Real-World Evidence: Current Best Practice for Reimbursement Decision-making. OHE Contract Research Report, London: Office of Health Economics. Available at: https://www.ohe.org/publications/real-world-evidence-current-best-practice/

Corresponding Author:
Sian Besley
sbesley@ohe.org

For further information please contact:

Professor Graham Cookson
Chief Executive, OHE
Honorary Visiting Professor in Economics at City, University of London

Tel +44 (0)207 747 1408
Email gcookson@ohe.org

About OHE Contract Research Reports

Many of the studies OHE Contract Research performs are proprietary and the results are not released publicly. Studies of interest to a wide audience, however, may be made available, in whole or in part, with the client's permission. They may be published by OHE alone, jointly with the client, or externally in scholarly publications. Publication is at the client's discretion.

Studies published by OHE as OHE Contract Research Reports are subject to internal quality assurance and undergo external review, usually by a member of OHE's Editorial Panel. Any views expressed are those of the authors and do not necessarily reflect the views of OHE as an organisation.

Funding and Acknowledgements

This contract research report was commissioned and funded by MSD.

Table of Contents

Executive Summary

Real-world data (RWD) is defined as data collected outside randomised control trials (RCTs) in real-world settings (FDA, 2018). RWD – the information – is transformed into real-world evidence (RWE) – the insight – through data analysis. This evidence can provide insights into the functioning of health technologies outside of clinical trial settings. Therefore, it could be a potentially useful tool for determining (cost-)effectiveness and utilisation of a technology in real-world settings, thereby providing additional information to inform reimbursement decision-making and facilitate patient access. However, this must be underpinned by appropriate and methodologically robust data analysis, as well as clear and transparent data governance, so that all stakeholders have trust in the interpretation of the data and in the important decisions that this RWE can inform. While there are many ways RWE can support health technology development, evaluation and adoption, this report focuses on key considerations for the use of RWE to assess clinical and comparative effectiveness and thereby inform reimbursement decisions made by Health Technology Assessment (HTA) bodies.

There are several challenges contributing to the underutilisation of RWE by HTA bodies. While RWD studies that assess comparative effectiveness have the potential for greater external validity than RCTs, the relatively lower internal validity and greater risk of bias means that there are concerns regarding its quality. This is compounded by a lack of transparency and often results in a lack of trust in RWE. In addition, decision-makers have not yet reached a consensus on what questions could be answered by RWE and what evidence is appropriate for answering these questions. In addition, many reimbursement decision-makers do not have the time and skillsets within their workforce to robustly generate and critically appraise RWE. This means that – without collaboration with other experts and a better understanding of the relevant considerations – decision-makers are at greater risk of making inappropriate reimbursement decisions, which may adversely impact patient access and, most importantly, health outcomes.

We conducted a targeted literature review to identify a set of core papers from well-established HTA bodies and highly cited literature that discuss best practices for RWE in reimbursement decision-making.

Trust needs to be established in RWE. Our research suggests that the current best practice for RWE studies that evaluate clinical effectiveness is to achieve this through the increased transparency and accountability that can be obtained in the short term by increasing the transparency in the publication of RWE. In the long run, the aim should be to pre-register RWD studies on a publicly available platform, where the registration should include a study protocol that contains a data analysis plan with any changes to this protocol being registered and justified. However, for this longer-term aim to be achieved, sufficient incentives for pre-registration are required, which could be provided by data owners, journal editors and/or HTA bodies who could make pre-registration compulsory for accessing their data for acceptance for publication and for inclusion in their decisions, respectively.

To incorporate RWE into reimbursement decision-making, HTA bodies need to establish a clear framework and process for generating and assessing RWE, which will involve reaching an agreement between relevant stakeholders on how the RWE generated in the specific local context is to be interpreted and applied. In addition, there is a need for appropriate channels and infrastructure for data access and analysis and a need to engage with multiple stakeholders to ensure HTA bodies have the capability to assess RWE as well as a transparent process that is open to scrutiny.

Our case study on RWE in Taiwan highlights that even with de-identifiable datasets being available and established registries, there are still opportunities for enhancing the collection of RWD and enabling more scientifically robust RWE generation. We suggest that this is needed before a consensus can be reached on the application of RWE in reimbursement decision-making.

The role that RWE should play in reimbursement decision-making is increasingly recognised. Several guidelines and frameworks have been produced and are welcomed, with recommendations coalescing around: (a) the need for data of a sufficient quality to answer the research question, (b) transparent evidence generation from planning through to study conduct and reporting, and (c) the use of analytical methods to minimise bias and appropriately characterise uncertainty. However, more needs to be done to ensure that the RWE used to inform decisions around patient access to medicines is appropriate, transparent and methodologically sound. We urge stakeholders internationally to work together to find the best solutions to advance our understanding and use of high-quality data collected in real-world settings, to aid interpretation and thereby promote trust in its use for reimbursement decision-making.

1. Introduction

The evidence used to support decision-making in health care is becoming ever more diverse. Increasingly, reimbursement decision-makers are faced with greater uncertainty at the time of market introduction, owing in some cases to accelerated regulatory approvals of novel technologies addressing unmet need. In addition, the importance of understanding the impact of healthcare interventions in real-world settings – which may differ from the outcomes achieved in randomised clinical trials (RCTs) – is being recognised (Berger et al., 2017; Chan K. et al., 2020; Garrison et al., 2007; Oortwijn, Sampietro-Colom and Trowman, 2019). `

Innovative technologies that work in new and complex ways are increasingly challenging the way that we assess new medicines for reimbursement. Advances in new treatment mechanisms – such as immuno-oncology (I-O), advanced therapy medicinal products (ATMPs), and precision medicine – are all examples that demonstrate the enhanced need and use of further data collection beyond clinical trials. Many novel technologies address a significant unmet medical need and target increasingly smaller patient populations, both of which may make clinical trial recruitment challenging and increase timelines, often making them unacceptably long (O'Donnell et al., 2020). Moreover, as ATMPs and other innovative therapies have the potential to offer long-term, durable effects, reimbursement decision-makers will be tasked with making approval decisions whilst there is still significant uncertainty in final outcomes (Aballéa et al., 2020; Coyle et al., 2020; Pearson, 2019; Hercher and Prince, 2018; van Overbeeke et al., 2021; Lloyd-Williams and Hughes, 2020; Faulkner et al., 2019; Garrison et al., 2021; Jørgensen and Kefalas, 2021; Qiu, Dabbous and Borislav, 2021; Ho et al., 2021; Persson and Norlin, 2020; Besley et al., 2022). Therefore, there is an important role for data collected alongside routine clinical practice to supplement and enhance our understanding of disease and long-term treatment effects.

Real-World Evidence (RWE) can provide decision-makers in the healthcare sector with insights into the functioning of health technologies outside of clinical trial settings. This includes providing regulatory and health technology assessment (HTA) bodies with (Berger et al., 2017):

- Descriptive analysis, e.g., disease epidemiology and treatment patterns
- Assessment of treatment safety through analysis of adverse events data
- Assessment of clinical and comparative effectiveness.

DEFINING REAL-WORLD DATA AND REAL-WORLD EVIDENCE

Real-world data (RWD) are data collected in real-life settings, i.e., data collected outside of randomised control trials (RCTs) (FDA, 2018), which could include data that are already routinely collected in a healthcare system (electronic health records, administrative reimbursement databases, pharmacy data etc.) or de-novo datasets that are set up to collect data for a particular observational study or pragmatic clinical trial (e.g., new patient registries for a disease or clinical procedure).

The use of RWD relies on a set of processes to collect, clean, manage, link and use the data within the context of country-specific frameworks for information governance (Cole et al., 2015). For RWD (the information) to be transformed into RWE (the insight), these processes must be credible and robust, and the data analysis must be appropriately designed, implemented and methodologically sound.

RWD studies that explore treatment effectiveness can be split into two categories: hypothesis evaluating treatment effectiveness (HETE) studies and exploratory studies. HETE studies involve the testing of a pre-specified hypothesis in a defined population, whilst exploratory studies are hypothesis-generating (Berger et al., 2017).

Based on the research objectives and right scoping, the feasibility of a proposed RWD study should be assessed in the local context.

While there are very many uses of RWD to support health technology development, evaluation and adoption, this report focuses on key considerations for the use of RWE to assess clinical and comparative effectiveness and thereby inform reimbursement decisions made by HTA bodies.

RCTs are HTA bodies' preferred source of evidence on efficacy (NICE, 2022; Pearson et al., 2018). However, RWE can fill gaps left by RCTs, including additional safety information; data on patient groups not included in the RCT; data on disease prevalence; functioning of the technology in a real-world setting; and providing comparisons to technologies or processes of care not included in the clinical trial. Pragmatic clinical trials – which investigate the effectiveness of technologies in real-world settings (Williams, Burden-Teh and Nunn, 2015), sit on the borderline between RCTs and RWE, and are a potential method for supporting evidence generation whilst improving generalisability.

RWE can enable better-informed patient access decisions by regulatory and HTA bodies. RWD is traditionally used by regulatory bodies to collect safety information on technologies with marketing authorisation (MA). More recently, RWE has been used to provide evidence in MA applications and indication extension (IE) decisions, with 39.9% of MA and 18.3% of IE applications in 2018-19 to the EMA, including RWE, of which 82.1% used RWE to provide safety information and 27% used RWE to provide evidence of efficacy (Flynn et al., 2022). In the US, the 21 Century Cures Act means that the Federal Drug Agency (FDA) must assess the use of RWE for IE applications and as a requirement for post-approval drug studies (Honigberg and Belson, 2020). The use of RWE in reimbursement decision-making by HTA bodies is in its infancy, but progress is being made.

In this paper, we will focus on reimbursement decisions made by HTA bodies when assessing health technologies. There are several opportunities for HTA bodies to incorporate RWE, including in determining initial reimbursement recommendations and coverage decisions; during re-assessment of technologies; and for informing and facilitating managed access or managed entry agreements (MEAs) such as coverage with evidence development or outcomes-based payment models.

Many HTA bodies accept RWE in submissions and consider this evidence in their decisions. 96% of submissions to the National Institute for Health and Care Excellence's (NICE) Cancer Drug Fund between April 2011 and October 2018 included RWE, of which the RWE was only completely rejected in 2 instances (Bullement et al., 2020). However, the quality of data sources was criticised, and NICE have since published a framework to try to improve the quality of RWE submitted for cost-effectiveness analyses (NICE, 2022), helping to communicate expected standards for RWE. A similar approach has been taken by Canada's Drug and Health Technology Agency (CADTH) which has recently released its own RWE draft guidance for consultation (CADTH, 2022b). While the use of RWE to inform reimbursement decisions is still relatively limited in Australia, there have been recent calls to enhance the use of RWE in this context and to develop clear standards for accepting RWE in regulatory and reimbursement evaluations (Medicines Australia, 2022).

This report summarises the key literature that sets out general best practices for RWE generation and current discussions surrounding the incorporation of RWE into reimbursement decisions. We believe that a global understanding and agreement around these standards is a necessary first step to ensuring the RWE produced is methodologically robust and that all stakeholders can trust in its appropriate use to optimise decision-making. As well as promoting good practice, a better global

understanding of the issues should reduce the risk of ill-informed reimbursement and patient access decisions based on poor quality RWE.

The findings of this report are founded upon a targeted literature review which identified materials produced by well-established HTA bodies and highly cited published literature, enabling us to define a set of core papers and documents that discuss current views on the use of RWE in reimbursement decision-making. The core papers cover several aspects of RWE generation, including methods for RWD collection and analysis, reporting of RWE, and key considerations for attempting to incorporate RWE into reimbursement decisions.

This report proceeds as follows: Section 2 outlines the key challenges for including RWE in reimbursement decision-making. Section 3 sets out how to establish trust in RWE, which is followed by Section 4, which discusses how RWE should be considered for incorporation into decision-making. Section 5 discusses the challenges and potential solutions in practice through a case study that assesses the use of RWE in reimbursement decisions in Taiwan. Finally, Section 6 concludes.

2. Challenges for the inclusion of RWE in decision-making

There are inherent differences between data collected in RCTs and RWD. The randomisation of treatments in RCTs leads to greater internal validity than effectiveness studies using RWD (i.e., fewer biases and greater strength of evidence), whilst RWD studies are likely to have more external validity (i.e., the results are likely to be more generalisable) (Chan K. et al., 2020). It is difficult to replicate the findings of RCTs in real-world settings, in particular the comparative effectiveness of technology, due to the challenges in controlling for both known and unknown confounding factors.

The relatively lower internal validity of RWD studies that aim to assess the effectiveness of a technology has resulted in concerns from decision-makers regarding the quality of the resulting RWE. RWD studies are prone to more bias and unmeasured confounding (Chan K. et al., 2020). This bias may result from not correcting for methodological issues such as measurement error, missing data and model misspecification, which result in endogeneity bias (Berger et al., 2017). There may also be publication bias: researchers and journal editors may choose not to publish unfavourable or insignificant results (Orsini et al., 2020). This means that the totality of evidence may not be available for consideration by decision-makers. Bias may also result from results-driven design modifications (Orsini et al., 2020) or 'data dredging' (Berger et al., 2017), where researchers amend their methodologies in the hope of obtaining more favourable or significant results.

In addition, the data quality concerns are further compounded by a lack of transparency in study design and the absence of data sharing. Decision-makers are, therefore, often not able to adequately assess the internal validity and quality of RWD studies. This leads to a lack of trust in RWE and subsequent low uptake in incorporating RWE into decisions. In addition, payers have expressed that RWE needs to be generated in a timelier fashion to enable it to be useful when making decisions (Pearson et al., 2018).

Furthermore, there has been no consensus from HTA bodies as to how and when RWE should be incorporated into reimbursement decisions (Chan K. et al., 2020). HTA bodies need to determine what questions they believe can be answered by RWE (Oortwijn, Sampietro-Colom and Trowman, 2019) and what data are appropriate for answering different types of research questions (Pearson et al., 2018). NICE describes some of the reasons why RCTs may not be available or why they may provide insufficient evidence for decision-making. They set out several 'use cases' for RWE, drawing on examples from past assessments (NICE, 2022). For example, NICE provides examples of using RWD to characterise health conditions, care pathways and patient outcomes in their Highly Specialised Technologies guidance (NICE, 2021a); estimating economic burden using linked RWD sets (NICE, 2019); designing and populating economic models (NICE, 2021b) as well as very many other examples including measuring patient experience, validating prognostic models, identifying health inequalities, estimating test accuracy, estimating procedure failure rates and measuring the impact of interventions on service delivery (NICE, 2022).

Without better sharing of information from some HTA bodies on the types of questions relevant to be addressed by RWE and what data are appropriate to answer them, it is difficult to generate RWE that will answer relevant questions in a way that is deemed acceptable by decision-makers. For studies of effectiveness, or where RWD are being used to validate or confirm clinical effectiveness, clarity on the definition, criteria and application of each real-world study endpoint should be determined and included in the study protocol with consensus across relevant stakeholders. For example, how is the real-world analysis compared to those reported from RCTs? Is it possible to robustly use real-world

comparative data in updating the local economic studies, such as local cost-effectiveness analysis of an innovation that has been reimbursed for a period? How could these comparisons be defined and interpreted in the re-evaluation of reimbursement decisions? Additionally, alignment from HTA bodies has the potential to enable RWD generation across countries that can be used in decisions by multiple decision-makers. This will be particularly important for rare diseases where patient populations are, by definition, small, and so collecting enough RWD to generate RWE is likely to require cross-country data collection (Besley et al., 2022).

The final challenge for the inclusion of RWE in decision-making relates to the knowledge of HTA bodies. There are likely to be many nuances to the data used to produce RWE. HTA bodies do not necessarily have the expertise within their workforce or committees to critically appraise RWE (Oortwijn, Sampietro-Colom and Trowman, 2019). Therefore, they need to find ways to collaborate with specialists, including those who captured and analysed the RWD, which may include individuals outside of the health sector (Oortwijn, Sampietro-Colom and Trowman, 2019). This, of course, should be paired with greater understanding from decision-makers themselves to provide them with the ability to assess common challenges that impact the quality of RWE. Without sufficient expertise, decision-makers are at a greater risk of making ill-informed reimbursement decisions which could inappropriately impact access for many patients.

3. Establishing Trust in RWE

Transparency in data collection and methods used to transform RWD to RWE would allow decision-makers – including HTA bodies – to assess the internal validity, quality, and suitability of RWE (Orsini et al., 2020; Wang et al., 2022), which is essential to establishing trust in the results.

Transparency facilitates the replication of results. If it is possible to track how RWD are collected and transformed into an RW dataset and then to RWE, then this enables the replication of the same methods to be employed on different data or different methods to be used on the same data to establish if the same conclusions are drawn (Berger et al., 2017; Pearson et al., 2018). This will instil confidence in the insights provided by analysis of RWD through decision-makers being able to determine that there have been no results-driven design modifications or 'data dredging.' It will also enable decision-makers to determine if replicability efforts have already been made by the creators of RWE.

3.1 Publication of results

Results of RWD studies, whether favourable or unfavourable, significant or insignificant, should be published. In reporting results, authors should explore and identify any methodological issues and potential sources of bias and discuss how these may impact the presented results (Orsini et al., 2020). Researchers should issue an attestation of conformance of deviation from any protocol published prior to conducting the RWD study (Berger et al., 2017; Orsini et al., 2020). This aims to enforce accountability and further enhance transparency.

Publication in peer-reviewed journals can be viewed as a proxy for the quality of the RWD study due to the review by an external expert and the need to share methods so they can be evaluated (Pearson et al., 2018). However, despite these requirements, sufficient details to enable reproducibility and trust to be established are often not met, leading to even published RWE not providing enough information to be appropriately assessed by HTA bodies, leaving them unable to consider the RWE in their decision-making. In addition, publication timelines often do not align with when RWE is of most value for decision-making, so assessment and verification of results by a third party may need to be used in the meantime (Pearson et al., 2018).

Despite this, publication in a peer-reviewed journal should remain the goal to ensure the availability of as much evidence generated in the public domain as possible, but transparency in the reporting of the methodology and limitations in results must be improved.

3.2 Pre-registration:

A culture of transparency should be established (Orsini et al., 2020). This is the aim of the Real-World Evidence Transparency Initiative, a partnership between ISPOR, the International Society for Pharmacoepidemiology, the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council (ISPOR, 2022). The initiative advises that RWD studies are pre-registered and that results are reported with sufficient methodological details. Further details are provided below. This is particularly relevant and important for RWD studies that assess effectiveness.

Pre-registration involves registering a trial or study prior to the commencement of analysis and is common for RCTs (Berger et al., 2017; Orsini et al., 2020). However, this process is yet to be widely

adopted for RWD studies that assess the effectiveness of a technology[1]. RWD study registries need to strike a balance between transparency and confidentiality (Berger et al., 2017). As discussed, transparency is desired to establish trust in RWE and improve its use in reimbursement decisions. However, the relatively lower costs of undertaking RWD studies mean that they have the potential to suffer from more 'scooping' of research ideas (where other researchers perform and publish the analysis before the original researchers) than RCTs (Orsini et al., 2020). This disincentivises researchers from pre-registering RWD studies. Therefore, a culture of transparency is unlikely to be achieved without sufficient incentives to pre-register RWD studies (Berger et al., 2017; Orsini et al., 2020).

There are several ways in which researchers could be incentivised to pre-register RWD studies (Orsini et al., 2020):

- Data owners could make pre-registration a condition of being able to use the data.
- Journal editors could make pre-registration a condition of publication.
- HTA bodies could make pre-registration a condition of using the resulting RWE in their reimbursement decision-making.

Currently, sufficient incentives are not being provided to make pre-registration of RWD studies common practice, and therefore, this approach to achieving transparency should be viewed as a long-term aim that will supplement the transparency in reporting of methodology and results in journal publications in the shorter term.

If sufficient incentives can be provided, any study protocols published as part of the pre-registration process should be published in the public domain. Publishing plans prior to conducting analysis enables decision-makers to see the original study intentions and proposed methods, thus enabling them to assess any divergences and post hoc amendments. Pre-registration also encourages deliberation, planning and accountability for those carrying out RWD studies (Berger et al., 2017). The NICE RWE framework, CADTH's provisional RWE guidance, and the REALISE (**REAL** World Data **I**n A**S**ia for H**E**alth Technology Assessment in Reimbursement working group) guidance highlight the importance of pre-registering studies on publicly available platforms, particularly for RWE generated to assess the comparative effectiveness of a treatment, with any changes being registered and justified (NICE, 2022; CADTH, 2022b; REALISE Working Group, 2021a).

RWD studies may be pre-registered on existing platforms. Orsini et al. (2020) outline criteria for evaluating if a pre-registration platform is suitable for HETE studies and provide – in their Appendix Table 1 – an assessment of the strengths and weaknesses of some existing databases for pre-registering RWD studies.

Study protocols need to contain enough information to provide the benefits outlined above. Following a protocol template will assist researchers in achieving this. If a common template is followed for all RWD study protocols, this will increase consistency across RWD studies and ensure protocols meet a set of core expectations (Wang et al., 2022). A joint task force between ISPOR (The Professional Society for Health Economics and Outcomes Research) and ISPE (The International Society for Pharmacoepidemiology) (part of the RWE transparency Initiative (ISPOR, 2022)) has developed a protocol for HETE studies using secondary data that aim to establish causal inference (Wang et al., 2022). The US Food and Drug Agency (FDA) is also creating a structured protocol and reporting template for RWD studies (Orsini et al., 2020).

Our literature search highlighted several important elements that should be included in a study protocol for RWD studies that assess effectiveness. Firstly, the protocol should declare the type of study that is being carried out, i.e., HETE or exploratory (Berger et al., 2017; Orsini et al., 2020), as this

[1] *The European Medicines Agency (EMA) requires or recommends study protocol pre-registration for observational post-authorization safety studies (PASS) (Wang et al., 2022).*

determines the broad approach that should be taken to the analysis of the RWD. For HETE studies, the hypothesis should be specified (Berger et al., 2017; Orsini et al., 2020). Research questions should be framed using PICOTS (Population, Interventions, Comparators, Outcomes, Timing and Setting) (Oortwijn, Sampietro-Colom and Trowman, 2019) with clear definitions for each variable provided under these elements. In addition, for studies using secondary data, it needs to be made clear the extent to which the process for selecting parameters and methods could have been influenced by a pre-look at the data (Orsini et al., 2020). Data analysis plans should also be shared. Any revisions to these protocols should be date-stamped (Orsini et al., 2020).

3.3 Information Governance

Beyond the mechanisms described for clear and transparent generation and publication of data, there is also a need to define robust processes for how data are accessed and credibly used through appropriate information governance. In 2015, OHE produced recommendations for an ideal governance framework for RWD, which encompassed recommendations and considerations for capturing the raw data, cleaning and managing the data, linkage and aggregation, and finally, access/use (Cole et al., 2015). According to the authors, the collection of data should be considered in the context of the prevailing data protection legislation, with due attention given to the most appropriate provisions around patient consent and/or alternative legal bases according to the intended use. Data controllers – the organisations responsible for collecting, managing, and linking patient data –must demonstrate strong and robust processes and meet quality criteria that give the public and data users confidence in the quality and security of the data held. There should be nationally agreed and implemented rules to optimise the interoperability of health record systems, and data linkage should be performed by a trusted third party.

De-identification and pseudonymisation of data can support the protection of personal information while permitting data linkage and, in some cases, data sharing, where appropriate security arrangements are in place for the protection of confidential patient data. These provisions for access should balance the protection of private information and the benefits that arise from using those data to inform important research. Where data can be completely anonymised, there is minimal risk to privacy, and data can be shared relatively freely. Requests for access to data containing patient-level identifying information (for example, to permit linkage across datasets) require the most scrutiny as the risk to privacy is greater. Models that could enable such use include capacity for in-house analysis by the data provider, permit access in a secure space which allows direct control and monitoring of data use, or through other solutions such as a distributed network model (Cole et al., 2015).

Appropriate and facilitative governance arrangements for RWE are imperative to facilitate evidence collection to meet the demands of regulators and HTA bodies and to make the most of healthcare information and the role it can play in improving patient care.

4. Inclusion of RWE in Reimbursement Decision-making

4.1 Overcoming barriers to including RWE in reimbursement decision-making

In order to incorporate RWE into reimbursement decisions, HTA bodies need to establish process infrastructure. This means ensuring they have both the capacity and capability to assess RWE. The latter will be best achieved through engagement with multiple stakeholders with expertise in the assessment of the value of RWE (Garrison et al., 2007). This is the approach of CADTH's Post-Market Drug Evaluation (PMDE) program. The program brings together multiple stakeholders, including experts in applied research, drug evaluation methodology and data analysis in a network that will produce responses based on RWE to questions and concerns from federal, provincial and territorial decision-makers regarding drugs approved for use in Canada (CADTH, 2022a).

Manufacturers, HTA bodies and other stakeholders should work together to develop a shared view of the role that RWE should play in reimbursement decision-making. They should also work together to produce data analysis and process standards (Pearson et al., 2018). In developing these standards, it will be important to recognise that evidence standards may differ depending on the type of decision that is being made (Pearson et al., 2018). For example, higher levels of rigour in evidence and process standards will be needed if the RWE is being used to: assert that a technology is superior to another treatment (i.e., more effective or cost-effective); that prices should be higher; that use should be expanded to a new indication; or that the decision will result in substantial changes to clinical practice that conflict an RCT or lack rationale. On the other hand, lower levels of rigour may be required if the RWE is to, for example: support a claim of lower cost for equal effectiveness in real-world settings; raise safety concerns; or support a decision that will not result in substantial changes to clinical practice or expand the use of the treatment (Pearson et al., 2018). This is due to the lower downside to the decision maker of making the wrong reimbursement decision based on the RWE in the latter scenarios. It should be noted that this does not advocate for lower quality of evidence (Pearson et al., 2018) but highlights that different types of evidence and levels of uncertainty may be accepted in different types of decisions.

Standards should be set by decision-makers and communicated to generators of RWE to ensure RWE generated is robust and provides meaningful information to decision-makers (Chan K. et al., 2020). This includes recommending appropriate methods for turning RWD into RWE and for overcoming methodological issues such as bias. This could also include publishing definitions of key outcomes, e.g., providing a definition of adherence (Pearson et al., 2018).

NICE's RWE framework explains where RWE could be used in decision-making and describes best practices for planning, conducting, and reporting RWD studies (NICE, 2022). Although this framework does not express minimum standards for the level of quality of RWE that NICE will accept, it does provide manufacturers and other producers of RWE with core principles and guidance that should enhance the quality of the RWE produced. The core principles include the following:

- ensuring data is of good provenance and that it is relevant and of sufficient quality to answer the research question;
- generation of evidence should be transparent with integrity from study planning through to study conduct and reporting; and

- the use of analytical methods that minimise the risk of bias and appropriately characterise the uncertainty.

Similarly, the REALISE working group has published non-compulsory guidance that aims to act as a framework for the production and use of RWE in decision-making in Asia, providing guidance aimed at 'generators of RWD' (REALISE Working Group, 2021b) and 'Doers of HTA' (REALISE Working Group, 2021a). They highlight the opportunities associated with using RWE, as well as the need to develop steps to mitigate erroneous data, standardise its collection, and ensure quality management and assurance.

The provisional CADTH guidance on RWE aims to harmonise RWE submission principles for Canadian HTA and regulators and to highlight important methodological considerations; this includes a submission checklist which notably includes information to assure data quality, including bias, confounding and effect modifiers/subgroup effects, as well as statistical methods and considerations around interpretation and generalisability (CADTH, 2022b).

4.2. How should RWE be incorporated into reimbursement decision-making?

A pre-requisite of incorporating RWE into reimbursement decision-making should be to ensure that the research questions and data are clinically relevant and meaningful. To support this, it is imperative that clinicians and/or medical societies have a role in defining the appropriate research questions, datasets, and items collected. While guidelines fall short of making specific recommendations on registry items and revisions – which will always be context specific – we would suggest that to maximise data quality and completeness, as well as coverage, datasets should be reviewed regularly to ensure the items collected are most appropriate and relevant to the research question. Furthermore, when planning primary data collection, this should be done in a patient-centred manner, collecting data that measures attributes and outcomes that are important to patients while minimising the burden on patients and healthcare professionals (NICE, 2022, p.6). Manufacturers are also likely to have a role to play in informing data collection relating to the performance of their products in a compliant and transparent way. Indeed, the ISPOR-ISPE special task force highlights that the involvement of key stakeholders (including patients, clinicians, clinical administrators, HTA/payers, regulators and manufacturers) is key for the meaningful design of RWD collection efforts (Berger et al., 2017).

RWE could be incorporated at all stages of reimbursement decision-making. This should include incorporating RWE into modelling projections when post-launch RWE is generated (Garrison et al., 2007). This may result in a change in the recommendation given by the HTA body, expansion in the indicators approved for reimbursement and/or a change in price.

Two fundamental principles underlay how RWE should be considered in reimbursement decision-making: consistency and transparency. Despite evidentiary standards having the potential to vary dependent on the question being answered by the RWE, the standards for assessing and including different types of RWE should be consistent. This means that RWE will be considered in a consistent manner across the assessment of different technologies (Garrison et al., 2007) to allow for consistent recommendations and final reimbursement decisions. If RWE is considered differently for a particular technology, then the rationale for this should be clear and communicated in the reporting of the outcome of the decision-making process.

HTA bodies should be transparent with regard to how they consider RWE in their decision-making process (Pearson et al., 2018). The process should be set out in their guidelines and should include what evidence requirements need to be met to initiate a reassessment of a technology and to

subsequently revise any initial reimbursement recommendations (Chan K. et al., 2020). In addition, HTA bodies should also be transparent about the role that RWE has played in the final decision outcome (Pearson et al., 2018). This involves communicating with all stakeholders the factors considered when reaching the decision. This will assure producers of RWE that it has been appropriately considered in reimbursement decisions.

While there is much discussion in the literature on the key processes and actions that researchers can take to ensure RWE stands up to scrutiny, guidance on how HTA bodies and their committees should actually interpret the results – in light of all the known challenges with RWD – is less well advanced. For example, it is a well-known phenomenon that drugs often fail to achieve the same outcomes in "real life" compared with those demonstrated in clinical trials: the so-called "efficacy-effectiveness" gap. Should there be a minimum performance level for RWE-determined comparative effectiveness for it to be deemed superior? Should this judgement be anchored in some way to the clinical trial results in order to judge the transferability of those trial results to what can be expected in real-world settings? The questions are very challenging and, in practice, will be context- and therapy-specific, but tackling these questions is needed to support decision-makers in their use of robust RWE to inform decisions.

5. Case Study: RWE in Taiwan

Taiwan is considered a leader in the Asia-Pacific region in terms of its approach to HTA. They have established infrastructure for collecting RWD, like many other countries, but unlike many other countries in the region, have demonstrated a willingness and ability to incorporate RWE into HTA decisions, as described in the REALISE guidance for 'doers of HTA' (REALISE Working Group, 2021). Nevertheless, there is some way to go to ensure all stakeholders are fully on board and satisfied with how RWE is used to support decision-making around patient access. Therefore, it offers an interesting case study to complement the general guidance described so far. This case study discusses further examples of the generation and application of RWE in Taiwan. We aim to provide insights into how the best practices outlined above could be implemented in practice to enhance the use of RWE in reimbursement decisions.

5.1 Overview of healthcare system and technology reimbursement

Taiwan's National Health Insurance (NHI) has provided universal health coverage to residents since 1995 (Wu, Majeed and Kuo, 2010). Insurance is mandatory for residents and provides comprehensive benefits and coverage. Taiwan's NHI is provided by a single insurer run by the government.

Since November 2007, Taiwan's Health Technology Assessment division of the Centre for Drug Evaluation (HTA/CDE) has been involved in the assessment of new technologies. In 2013, the passing of the second-generation NHI Act resulted in changes to the drug listing policy. An explicit deliberation framework was established, which incorporates four critical factors: individual's health, medical ethics, treatment cost-effectiveness, and insurance finances. Following this introduction, a 2 -tier appraisal strategy was introduced: 1) HTA/CDE gathers evidence in a systematic manner based on the new drug deliberation framework, 2) the Pharmaceutical Benefit and Reimbursement Scheme (PBRS) Joint Committee enable wider engagement from relevant parties such as patient groups.

RWD IN TAIWAN
The National Health Insurance Research Database (NHIRD) collects information on NHI claims in Taiwan. The NHIRD – owned by the NHIA (National Health Insurance Administration) – has been extensively linked to national registries and national surveys, thus providing a rich source of RWD and established processes for their collection (REALISE Working Group, 2021a). Further, their data governance has been enhanced through the creation of the Health and Welfare Data Centre (HWDC) to strengthen the protection of claims data (REALISE Working Group, 2021a). De-identified and anonymized patient data should be accessible to researchers and industry with prior approval of the project by the Institutional Review Board (IRB) (REALISE Working Group, 2021a), though it is unclear the extent to which this has happened in practice.

5.2 The current use of RWE in reimbursement decisions

The use of managed entry agreements (MEAs) in Taiwan is expanding, and with it, the endorsement and use of RWE for new drug appraisals (National Health Insurance Administration, 2018),

Patient registries can be used to facilitate RWD collection for outcome-based MEAs. When existing databases are not available or do not capture the required information on clinical safety and/or treatment effectiveness, it may be necessary to develop a new patient registry. For example, a new

registry was developed to collect treated patient outcomes to support the outcomes-based MEA for a direct-acting antiviral (DAA) drug for the treatment of hepatitis C (Hong et al., 2021; ICH GCP, 2023). This was the first outcomes-based MEA between the NHIA and pharmaceutical companies (in effect from 2017 to 2018) and dictated that the NHIA would only reimburse prescriptions that resulted in a clinically significant patient outcome, namely a sustained virological response for 12 weeks (SVR12). The NHIA and the National Hepatitis C Program (NHCP) office collect the RWD and manage the NHI DAA-treated patients registry.

When practitioners apply for prescriptions that require prior authorization from the NHIA, they must provide the patients baseline clinical data such as measurement of biomarkers and the genotypes of the hepatitis C virus. Following treatment, physicians are mandated to submit patients' SVR12 along with any adverse events (AEs) in order to claim for the costs of the treatment to be reimbursed. To measure effectiveness in the real world, the NHCP produced routine reports, which document the reasons for treatment discontinuation, treatment safety, and the SVR12 and are disclosed on the Ministry of Health and Welfare's (MoHW) website (Ministry of Health and Welfare, 2022). An assessment of the real-world effectiveness of DAAs has also been published in peer-reviewed journals, including by Hong et al. (2020) and Chen et al. (2021)

The Taiwan Food and Drug Administration (TFDA)'s marketing authorisation resulted in comprehensive coverage of the DAA. In the NHI DAA-treated patients registry, data are collected to assess whether reimbursement criteria are met, but also predefined baseline characteristics (e.g., severity, RNA type) and predictive factors in this therapeutic area, making it also possible to conduct a comparative effectiveness analysis across technologies.

A further example of a registry used to support an MEA can be seen in the patient registry for IO, which was developed in 2019 to capture RWD on immunologic agents (immune checkpoint inhibitors or ICIs) covering ten indications across eight different cancer types (National Health Insurance Administration, 2019a; b). The PBRS Joint Committee approved these ICIs for use under the condition that patient biomarkers, clinical effectiveness and severe side effects of the treatments will be collected with the reimbursement and coverage decisions and actual utilisation and cost data being assessed by the NHIA a year later. The concept is similar to the coverage with evidence development program in the UK (Diaby and Goeree, 2016): the collection of RWD and the generation of RWE start at the initial reimbursement of the technology to handle clinical/financial uncertainty surrounding a reimbursement decision. In practice, clinical practitioners who want to prescribe ICIs for their patients are requested to submit the baseline characteristics, biomarker presentence, and cancer diagnoses of potential users to get prior-prescription authorization. To be reimbursed for the treatment, clinical practitioners are asked to submit the treatment outcomes of reimbursed users. The RWD was evaluated by the CDE/HTA, and executive summaries were published on the NHIA's website (National Health Insurance Administration, 2019a).

Since 1st April 2020, the NHIA lowered the coverage of the ICIs for metastasized gastric adenocarcinoma and advanced or metastatic hepatocellular carcinoma due to the RWE provided by the CDE/HTA demonstrating relatively poor effectiveness for these cancers in real-world settings in Taiwan, confirmed by the NHI expert meeting (National Health Insurance Administration, 2019b). This is unsurprising given that the restricted reimbursement criteria for IO during the period of RWD collection meant that the observed patients in clinical practice through the IO registry were literally different from the trial population. This means that the failure of the RWE to reproduce treatment outcomes demonstrated in the RCT was not simply due to the efficacy-effectiveness gap – but (also) because of the differing patient characteristics and confounders that could not be identified and results adjusted for.

5.3 Challenges for the inclusion of RWE in reimbursement decisions

There are three key challenges to the inclusion of RWE in reimbursement decisions in Taiwan.

Firstly, the underlying aim of NHIA for incorporating RWE into reimbursement decisions is currently ambiguous, meaning that HTA bodies and other stakeholders have not developed a shared view of the role that RWE should play in reimbursement decision-making. Without a transparent aim, there may be a perception that RWE – and its use in MEAs to determine eligibility for reimbursement – is driven by financial management rather than to improve the quality of care and patient outcomes. Although reimbursement decisions should consider the financial implications of reimbursing a treatment for a specific indication, not also considering the broader role that RWE could play in reimbursement decisions could mean that patients lose out in the long run.

The second challenge relates to data ownership and the conversion of RWD into RWE. The current model of NHIA-owned patient registries being used to collect and analyse RWD for reimbursement decisions means that the process and methods are not fully disclosed or transparent to relevant stakeholders such as clinicians, medical societies, academic researchers, patient groups and manufacturers, who cannot, therefore, contribute their expertise to the optimal use or assessment of those data. In other words, the RWE generation is not independently validated nor assessed via an open consensus framework. Therefore, there is still significant room for improvement to be made to ensure transparency in methodology and results and to realise the benefits of multi-stakeholder engagement.

Finally, despite Taiwan having several well-established patient registries, there are still improvements to be made. The registries need to be updated to ensure that clinicians are able to provide required inputs and tailor the data in order to ensure it is as relevant as possible to clinical practice for the indication under consideration while maintaining consistency across sites. Requiring data to be inputted that is redundant or outdated is an inefficient use of clinicians' time and lowers compliance and the reliability of data reporting. Moreover, there is no established procedure for external quality assurance and quality control.

5.4 Key local needs to appropriate implementation

Taiwan has sufficient infrastructure to generate and incorporate quality RWE into reimbursement decisions. This represents a huge opportunity that is not yet being fully capitalised. To enhance the use of RWE, we present a number of opportunities that will facilitate better implementation of RWE in decision-making in Taiwan.

The recommendations that we make in this section align with the ambition to enhance the use and utility of RWD to inform RWE in reimbursement decisions. Like most countries, the case for the appropriate use of RWD in Taiwan is getting stronger. It is important to capitalize on the learnings of other countries, and our recommendations here align with the global experience and advice to date.

1. **INFRASTRUCTURE:**

On the shoulder of the REALISE guidance (REALISE Working Group, 2021b), national guidance should be further elaborated through engagement with all stakeholders, including governmental officers, reimbursement decision-makers, HTA reviewers, medical societies, academic professors/researchers, patient groups, and manufacturers. This is the first step of creating a coalition for RWE. Most important of all, the Taiwan-specific guidance could also help to align the

underlying aims of NHIA and HTA bodies, for example incorporating RWE into reimbursement decisions.

To enhance Taiwan's RWE infrastructure, an independent RWE steering committee reporting to the MoHW could also be established to ensure the integrity of the RWE generated and the appropriateness of its use in reimbursement decisions. This is the approach of the CADTH PMDE program, where a network of external experts brings together evidence to answer questions raised by decision-makers on post-marketing drug safety and effectiveness (CADTH, 2022a). This external committee should also help establish core values for the generation and inclusion of RWE in reimbursement decisions and ensure that these are adhered to.

In addition, the data collected in existing patient registries should be reviewed regularly to ensure that sufficient relevant data is collected that makes efficient use of clinicians' time. To achieve this, greater input from experts should be sought in the design and maintenance of registries. An RWE working group could be established as a hub to work with medical experts in different therapeutic areas. Medical societies/professionals can help to design registries, review reports, and identify therapeutic areas that could potentially benefit from a registry alongside the working group. A good practice example is offered by the NHCP office, which successfully updates the columns of the NHI DAA-treated patient registry in a timely manner, ensuring the collection of all relevant data to support the RWE generation because of a close collaboration with medical societies. We envisage a regular review of registries to eliminate the collection of unnecessary data variables while enhancing data completeness and quality; we would suggest this takes on at least an annual basis, especially in the case of new medicines for rapidly evolving therapeutic areas.

2. CONSISTENCY AND TRANSPARENCY

Ensuring a consistent process for RWE generation, including communicating the aims of including RWE and the open sharing of reports that detail how the RWE has contributed to a reimbursement decision, should be the basis for a transparent, fair, and robust HTA system. Learning from the NICE's real-world evidence framework (NICE, 2022) could support such efforts, and involving multiple stakeholders in improving these processes could ensure an approach that balances the aims of all stakeholders. As previously mentioned, national RWE guidance could facilitate the production of RWE that is fit for purpose and relevant to the Taiwanese national context.

Generators of RWE should also work towards ensuring they contribute towards establishing a culture of transparency and consistency in the detailed reporting of their methods and results. As levels of rigour in evidence and process standards will be adjusted depending on the study objective, especially for the questions around comparative effectiveness in the real-world setting, a proper set of methodologies to adjust for bias and confounding factors is needed to promote scientific rigour. These should be transparently communicated. In the long run, the publication of a clear specific study protocol, including a statistical analysis plan and interpretation, should be reviewed and approved by the officially appointed Working Group for each evaluation project, which could be for a specific molecule or a class of molecules. Predefined study objectives should also be included, as well as predefined thresholds to judge acceptable response rates (level of effectiveness).

3. REPRODUCIBILITY

The NHIA and HTA bodies should highlight the importance of scientific rigour in the use of RWE, especially when used to revise or overturn access or reimbursement recommendations. Pre-registration of RWE studies (particularly for those that assess effectiveness), publication of analytic methods and results are important and would engender greater trust in the results, as well as develop a culture of transparency in Taiwan.

Releasing patient registry datasets, while assuring appropriate information governance and data confidentiality provisions (such as what already occurs with the NHI research database) could be considered to improve both the reproducibility and transparency of data practices. This could enable academic researchers, medical societies, and physicians not only to scrutinize data but also to further investigate potential factors behind trends, generate hypotheses, and inspire future research studies.

4. STAKEHOLDERS' INVOLVEMENT

Multiple stakeholders should be involved at all stages of RWE generation and appraisal, as already discussed, including patients, clinicians, clinical administrators, HTA/payers, regulators, and manufacturers.

Patient groups can contribute their perspectives to improve the design of patient registries and ensure comprehensive records are collected to reflect the disease burden and potential treatment benefits, helping to realise the 'patient-centred' approach suggested in the NICE RWE guidance (NICE, 2022). In the preliminary analysis, patient groups can help to interpret the analytic result and underlying confounding factors. For example, patient groups can point out the reason for low adherence and give the payer an opportunity to remove health system access barriers in a timely manner. In the appraisal process, patients' views should inform the measured value of clinical improvement and help all stakeholders to understand patients' viewpoints. Manufacturers can also play a role in RWE collaborations, for example, helping to facilitate the establishment of registries, advancing analytic methodologies, and supporting international efforts to pool data across countries to enhance the statistical power of RWD.

SUMMARY

Overall, there has been tremendous progress in Taiwan in terms of collecting RWD that can shed light on the effectiveness of medical interventions in real-life settings and work towards a learning health care system. Based on the guidance offered by the key international literature, described in sections 2 to 4 of this report, there may be some areas for improvement in the application and use of RWD to inform reimbursement decisions in Taiwan. These include: continuing to improve the data infrastructure; promoting consistency, transparency and reproducibility in RWE; and ensuring broad stakeholder involvement to leverage the unique insights and skills that these different groups can offer.

6. Conclusion

In this paper, we have summarised the key themes in the literature to date, highlighting current advice on best practices for RWE. RWE can provide valuable insights into the functioning of technologies and diseases in real-world settings. Understanding of the potential role of RWE in facilitating appropriate access to novel medicines has expanded over recent years. This momentum has been inspired by the strong pipeline of new innovative medicines with a huge promise of transformational benefits, for which standard routes of evidence development are not always feasible or where uncertainty over benefits remains.

Appropriate use of RWE can help bridge this gap, but to have trust in the insights it can provide, we need confidence in the methods and processes applied through its generation and use. A culture of transparency in evidence generation is needed – from study planning through to conduct and reporting – to enable trust in the RWE and in the decisions that it engenders. In addition, data quality needs to be sufficient to answer the research question, and RWE generators, as well as decision-makers, should use appropriate analytical methods to minimise bias and characterise uncertainty.

Our Taiwan case study demonstrates that RWD is often not being collected and utilised to its full potential, with opportunities remaining to capitalise on the existing data infrastructure, enhance consistency and transparency in data use, promote scientific rigour by ensuring reproducibility, and improve stakeholder involvement.

Guidelines published by HTA bodies are very welcome – helping to build towards a shared understanding of appropriate principles and practice and providing a start to developing consistency and transparency in the generation and use of RWE. Less progress has been made on how to interpret RWE to optimise decision-making. This requires a greater understanding from decision-makers on how to assess the quality of RWE but also requires a clear and deliberative approach to determining what constitutes acceptable performance in real-life settings. This is likely to be therapy- and context-specific, but establishing broad principles should be a key focus of further research.

We recognise that our review was not extensive, instead focusing on material from well-established HTA bodies and highly cited literature, but we believe that our findings characterise the key issues and next steps for the inclusion of RWE in HTA decisions.

As highlighted by the literature and our Taiwan case study, we believe the way forward involves engagement from multiple stakeholders. We urge stakeholders internationally to work together to find the best solutions to advance our understanding and use of high-quality data collected in real-world settings, to aid interpretation and thereby promote trust in its use for reimbursement decision-making.

References

Aballéa, S., Thokagevistk, K., Velikanova, R., Simoens, S., Annemans, L., Antonanzas, F., Auquier, P., François, C., Fricke, F.-U., Malone, D., Millier, A., Persson, U., Petrou, S., Dabbous, O., Postma, M. and Toumi, M., 2020. Health economic evaluation of gene replacement therapies: methodological issues and recommendations. *Journal of Market Access & Health Policy*, 8(1), p.1822666. 10.1080/20016689.2020.1822666.

Berger, M.L., Sox, H., Willke, R.J., Brixner, D.L., Eichler, H.-G., Goettsch, W., Madigan, D., Makady, A., Schneeweiss, S., Tarricone, R., Wang, S.V., Watkins, J. and Daniel Mullins, C., 2017. Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making. *Pharmacoepidemiology and Drug Safety*, 26(9), pp.1033–1039. 10.1002/pds.4297.

Besley, S., Henderson, N., Towse, A. and Cole, A., 2022. *Health Technology Assessment of Gene Therapies: Are Our Methods Fit for Purpose?* [online] Available at: https://www.ohe.org/publications/health-technology-assessment-gene-therapies-are-our-methods-fit-purpose [Accessed 15th July 2022].

Bullement, A., Podkonjak, T., Robinson, M.J., Benson, E., Selby, R., Hatswell, A.J. and Shields, G.E., 2020. Real-world evidence use in assessments of cancer drugs by NICE. *International Journal of Technology Assessment in Health Care*, pp.1–7. 10.1017/S0266462320000434.

CADTH, 2022a. *CADTH Post-Market Drug Evaluation Proposal: Program Overview*. [online] Available at: https://www.cadth.ca/sites/default/files/attachments/2022-09/PMDE%20Program%20Overview_%20v1.1%20DRAFT%20-%20Final.pdf .

CADTH, 2022b. *RWE Reporting Guidance - Draft for Consultation*. [online] Available at: https://www.cadth.ca/news/cadth-launches-consultation-real-world-evidence-reporting-guidance .

Chan K., Nam S., Evans B., Deoliveira C., Chambers A., Gavura S., Hoch J., Mercer R.E., Dai W.F., Beca J., Tadrous M., and Isaranuwatchai W., 2020. Developing a framework to incorporate real-world evidence in cancer drug funding decisions: The Canadian Real-world Evidence for Value of Cancer Drugs (CanREValue) collaboration. *BMJ Open*, 10(1), p.e032884. 10.1136/bmjopen-2019-032884.

Cole, A.M., Garrison, L.P., Mestre-Ferrandiz, J. and Towse, A., 2015. *Data Governance Arrangements for Real-World Evidence*. [OHE Consulting Report] London: Office of Health Economics. Available at: https://www.ohe.org/publications/data-governance-arrangements-real-world-evidence .

Coyle, D., Durand-Zaleski, I., Farrington, J., Garrison, L., Graf von der Schulenburg, J.-M., Greiner, W., Longworth, L., Meunier, A., Moutié, A.-S., Palmer, S., Pemberton-Whiteley, Z., Ratcliffe, M., Shen, J., Sproule, D., Zhao, K. and Shah, K., 2020. HTA methodology and value frameworks for evaluation and policy making for cell and gene therapies. *The European Journal of Health Economics*, 21(9), pp.1421–1437. 10.1007/s10198-020-01212-w.

Diaby, V. and Goeree, R., 2016. Coverage with Evidence Development in Comparative Effectiveness Research. In: A. Levy and B. Sobolev, eds., *Comparative Effectiveness Research in Health Services*, Health Services Research. [online] Boston, MA: Springer US, pp.1–16. 10.1007/978-1-4899-7586-7_17-1.

Faulkner, E., Spinner, D.S., Ringo, M. and Carroll, M., 2019. Are Global Health Systems Ready for Transformative Therapies? *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 22(6), pp.627–641. 10.1016/j.jval.2019.04.1911.

FDA, 2018. *FRAMEWORK FOR FDA'S REAL-WORLD EVIDENCE PROGRAM*. [online] Available at: https://www.fda.gov/media/120060/download#:~:text=For%20the%20purposes%20%20of%20this%20framework%2C%20FDA,Evidence%20%28RWE%29%20is%20the%20clinicalevidence%20about%20the%20usage .

Flynn, R., Plueschke, K., Quinten, C., Strassmann, V., Duijnhoven, R.G., Gordillo-Marañon, M., Rueckbeil, M., Cohet, C. and Kurz, X., 2022. Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence? *Clinical Pharmacology & Therapeutics*, 111(1), pp.90–97. 10.1002/cpt.2461.

Garrison, L.P., Neumann, P.J., Erickson, P., Marshall, D. and Mullins, C.D., 2007. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value in Health*, 10(5), pp.326–335. 10.1111/j.1524-4733.2007.00186.x.

Garrison, L.P., Pezalla, E., Towse, A., Yang, H., Faust, E., Wu, E.Q., Li, N., Sawyer, E.K. and Recht, M., 2021. Hemophilia Gene Therapy Value Assessment: Methodological Challenges and Recommendations. *Value in Health*, 24(11), pp.1628–1633. 10.1016/j.jval.2021.05.008.

Hercher, L. and Prince, A.E.R., 2018. Gene Therapy's Field of Dreams: If You Build It, Will We Pay Legal, Ethical, and Policy Implications of New Gene-Editing Technologies. *North Carolina Law Review*, 97(5), pp.1463–1496.

Ho, J.K., Borle, K., Dragojlovic, N., Dhillon, M., Kitchin, V., Kopac, N., Ross, C. and Lynd, L.D., 2021. Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review. *PharmacoEconomics*, 39(9), pp.995–1019. 10.1007/s40273-021-01051-4.

Honigberg, R. and Belson, N., 2020. *Contemporary Applications of Real-World Evidence in Regulatory Decision Making: A Case Series Review*. [online] Available at: https://medicalaffairs.org/wp-content/uploads/2020/10/RWE-Contemporary-Aplications-V2.pdf .

ISPOR, 2022. *ISPOR - Real-World Evidence Transparency Initiative*. [online] Available at: https://www.ispor.org/strategic-initiatives/real-world-evidence/real-world-evidence-transparency-initiative [Accessed 12th December 2022].

Jørgensen, J. and Kefalas, P., 2021. The use of innovative payment mechanisms for gene therapies in Europe and the USA. *Regenerative Medicine*, 16(4), pp.405–422. 10.2217/rme-2020-0169.

Lloyd-Williams, H. and Hughes, P.D., 2020. HTA OF ADVANCED THERAPY MEDICINAL PRODUCTS. *Centre for Health Economics and Medicines Evaluation*, p.56.

Medicines Australia, 2022. *Real world evidence: Australia needs standards for accepting real world evidence in regulatory and reimbursement evaluations*. [online] Available at: https://www.medicinesaustralia.com.au/wp-content/uploads/sites/65/2022/11/HTA-DP-Real-World-Evidence-.pdf [Accessed 12th January 2023].

National Health Insurance Administration, M. of H. and W., 2018. *The addition of relevant regulations of the Managed Entry Agreement (MEA)*. [文字] 衛生福利部中央健康保險署. Available at: https://www.nhi.gov.tw/News_Content.aspx?n=FC05EB85BD57C709&s=FCE5D1753D1BF7C2&Create=1 [Accessed 23rd November 2022].

National Health Insurance Administration, M. of H. and W., 2019a. *Questions and answers on the payment of the immuno-oncology*. [文字] 衛生福利部中央健康保險署. Available at: https://www.nhi.gov.tw/content_list.Aspx?N=7157a9a3e2a3b110&topn=3fc7d09599d25979&Create=1 [Accessed 23rd November 2022].

National Health Insurance Administration, M. of H. and W. in T., 2019b. *The reimbursement policy of immune checkpoint inhibitors*. [文字] 衛生福利部中央健康保險署. Available at: https://www.nhi.gov.tw/content_list.Aspx?N=7157a9a3e2a3b110&topn=3fc7d09599d25979&Create=1 [Accessed 23rd November 2022].

NICE, 2019. *Overview | Benralizumab for treating severe eosinophilic asthma | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/ta565 [Accessed 21st December 2022].

NICE, 2021a. *Overview | Onasemnogene abeparvovec for treating spinal muscular atrophy | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/hst15 [Accessed 21st December 2022].

NICE, 2021b. *Overview | QAngio XA 3D QFR and CAAS vFFR imaging software for assessing coronary stenosis during invasive coronary angiography | Guidance | NICE*. [online] Available at: https://www.nice.org.uk/guidance/dg43 [Accessed 21st December 2022].

NICE, 2022. NICE real-world evidence framework. [online] Available at: https://www.nice.org.uk/corporate/ecd9/chapter/overview .

O'Donnell, J.C., Le, T.K., Dobrin, R., Higashi, M., Pereira, A., Wagner, S., Yang, A. and Hukkelhoven, M., 2020. Evolving use of real-world evidence in the regulatory process: a focus on immuno-oncology treatment and outcomes. *Future Oncology*. [online] 10.2217/fon-2020-0591.

Oortwijn, W., Sampietro-Colom, L. and Trowman, R., 2019. How to Deal with the Inevitable: Generating Real-World Data and Using Real-World Evidence for HTA Purposes – From Theory to Action. *International Journal of Technology Assessment in Health Care*, 35(4), pp.346–350. 10.1017/S0266462319000400.

Orsini, L.S., Berger, M., Crown, W., Daniel, G., Eichler, H.-G., Goettsch, W., Graff, J., Guerino, J., Jonsson, P., Lederer, N.M., Monz, B., Mullins, C.D., Schneeweiss, S., Brunt, D.V., Wang, S.V. and Willke, R.J., 2020. Improving Transparency to Build Trust in Real-World Secondary Data Studies for Hypothesis Testing—Why, What, and How: Recommendations and a Road Map from the Real-World Evidence Transparency Initiative. *Value in Health*, 23(9), pp.1128–1136. 10.1016/j.jval.2020.04.002.

van Overbeeke, E., Michelsen, S., Toumi, M., Stevens, H., Trusheim, M., Huys, I. and Simoens, S., 2021. Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions. *Drug Discovery Today*, 26(2), pp.399–415. 10.1016/j.drudis.2020.11.024.

Pearson, L., 2019. *Early Experience with Health Technology Assessment of Gene Therapies in the United States: Pricing and Paying for Cures*. [online] Available at: https://www.ohe.org/publications/early-experience-health-technology-assessment-gene-therapies-united-states-pricing-and [Accessed 20th October 2021].

Pearson, S.D., Dreitlein, W.B., Towse, A., Hampson, G. and Henshall, C., 2018. *A framework to guide the optimal development and use of real-world evidence for drug coverage and formulary decisions | Journal of Comparative Effectiveness Research*. [online] Available at: https://www.futuremedicine.com/doi/10.2217/cer-2018-0059 [Accessed 12th October 2022].

Persson, U. and Norlin, J., 2020. Opportunities and Challenges of an Innovative Payment Model for Advanced Medicinal Products in Sweden - A Hypothetical Example in the Treatment of B-thalassemia. *IHE Report*, 3, p.29.

Qiu, T., Dabbous, M. and Borislav, B., 2021. *The Evaluation of Pivotal Trials for Advanced Therapies From Regulatory and Health Technology Assessment Perspectives in Europe*. [online] ISPOR | International Society For Pharmacoeconomics and Outcomes Research. Available at: https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/challenges-in-precision-medicine-aiming-to-align-data-value-and-costs/the-evaluation-of-pivotal-trials-for-advanced-therapies-from-regulatory-and-health-technology-assessment-perspectives-in-europe [Accessed 1st November 2021].

REALISE Working Group, 2021a. *For Doers of HTA: HTA Agencies and HTA Researchers. Use of Real-World Data and Real-World Evidence to Support Drug Reimbursement Decision-Making in Asia.* [online] Available at: https://hiper.nus.edu.sg/realise-guidance/ [Accessed 6th December 2022].

REALISE Working Group, 2021b. *For Generators of RWD: Clinicians and Hospital Research Staff. Use of Real-World Data and Real-World Evidence to Support Drug Reimbursement Decision-Making in Asia.* [online] Available at: https://hiper.nus.edu.sg/realise-guidance/ [Accessed 6th December 2022].

Wang, S.V., Pottegård, A., Crown, W., Arlett, P., Ashcroft, D.M., Benchimol, E.I., Berger, M.L., Crane, G., Goettsch, W., Hua, W., Kabadi, S., Kern, D.M., Kurz, X., Langan, S., Nonaka, T., Orsini, L., Perez-Gutthann, S., Pinheiro, S., Pratt, N., Schneeweiss, S., Toussi, M. and Williams, R.J., 2022. HARmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects: A Good Practices Report of a Joint ISPE/ISPOR Task Force. *Value in Health*, 25(10), pp.1663–1672. 10.1016/j.jval.2022.09.001.

Wu, T.-Y., Majeed, A. and Kuo, K.N., 2010. An overview of the healthcare system in Taiwan. *London Journal of Primary Care*, 3(2), pp.115–119.

About us
Founded in 1962 by the Association of the British Pharmaceutical Society, the Office of Health Economics (OHE) is not only the world's oldest health economics research group, but also one of the most prestigious and influential.

OHE provides market-leading insights and in-depth analyses into health economics & health policy. Our pioneering work informs health care and pharmaceutical decision-making across the globe, enabling clients to think differently and to find alternative solutions to the industry's most complex problems.

Our mission is to guide and inform the healthcare industry through today's era of unprecedented change and evolution. We are dedicated to helping policy makers and the pharmaceutical industry make better decisions that ultimately benefit patients, the industry and society as a whole.

OHE. For better healthcare decisions.

Areas of expertise

- Evaluation
- The economics of health care systems
- Health technology assessment (HTA) methodology and approaches
- HTA's impact on decision-making, health care spending and the delivery of care
- Pricing and reimbursement for biologics and pharmaceuticals, including value-based pricing, risk sharing and biosimilars market competition
- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

CONTRACT RESEARCH REPORT
MAY 2023

ohe.org

The Office of Health Economics A Company Limited by Guarantee of Registered No.09848965
OHE Consulting Ltd Registered Company No.09853113
OHE is a Charity Registration No.1170829
Registered Office 2nd Floor Goldings House, Hay's Galleria, 2 Hay's Lane, London, SE1 2HB