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Real-World Evidence and Health Technology Assessment Decision-Making

What agencies — and their biopharma stakeholders — need to know

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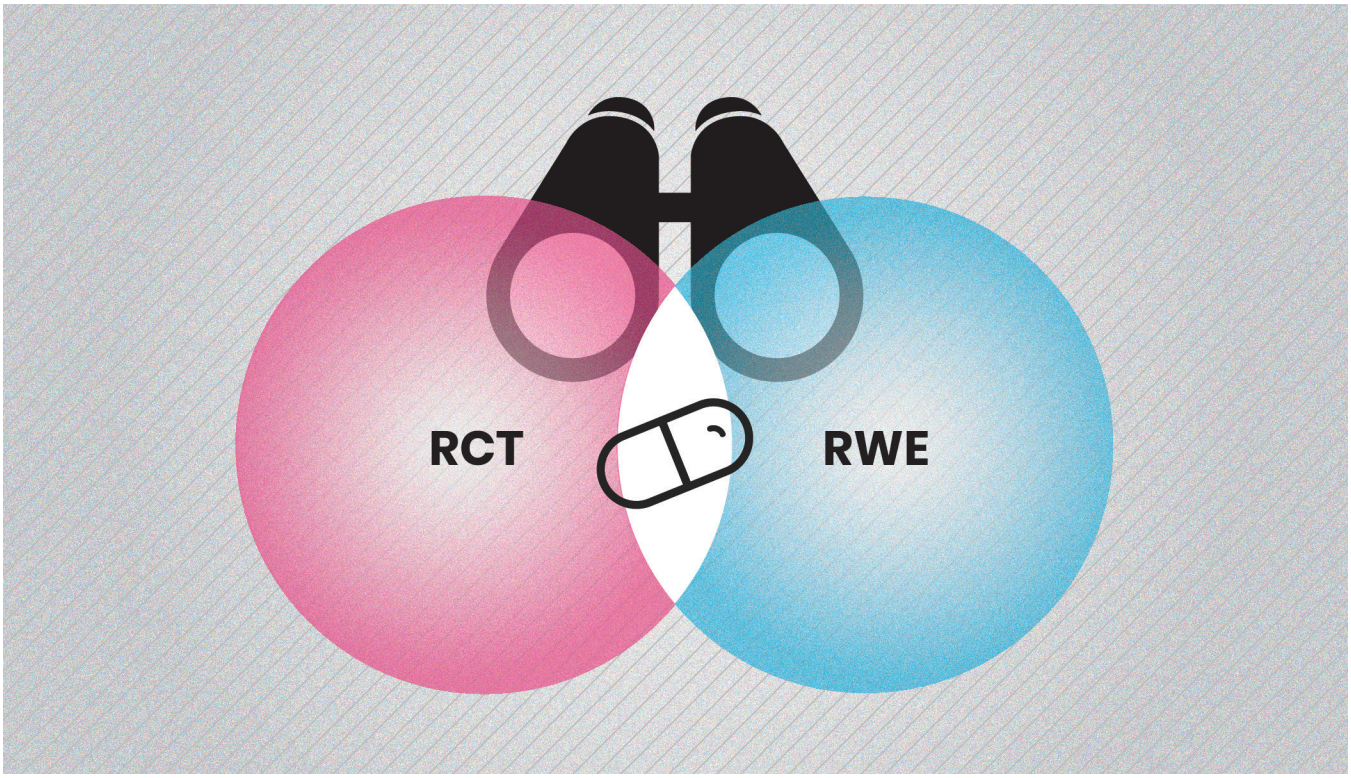


In most instances, health technology assessment (HTA) agencies require and rely on randomized controlled trial (RCT) data in their evaluations. However, this leaves what the industry has termed the efficacy-effectiveness gap. How will a drug that worked in a clinical trial work in clinical practice?

While RCTs have excellent internal validity (due to homogeneous patient populations and very controlled circumstances), their generalizability to clinical practice is questionable, which leaves HTAs in a difficult position. The good news is that real-world evidence (RWE) can bridge this gap by evaluating a drug in current clinical practice, with current standards of care, and in the relevant patient populations. In this white paper, we explore the current state of RWE adoption by HTAs, opportunities for increased use of observational data, and the implications for biopharma.

"Real-world evidence is not a substitute for a well-conducted controlled trial, but there are many situations where you cannot do a well-controlled trial. In those situations, you really want RWE to complement your clinical data, for example, through external control arms."

JENS GRUEGER, PhD

Affiliate Professor at the University of Washington, former Head of Global Access at Roche, and President-elect of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)*

* Dr. Jens Grueger's comments are his personal opinions and do not reflect the position of ISPOR.

The role of HTA agencies

HTA agencies are bodies that assess how valuable a specific health technology will be in and to their healthcare system, and for some HTA agencies, its cost-effectiveness.

What is HTA?
The World Health Organization refers to HTA as "the systematic evaluation of properties, effects, and/or impacts of health technology." HTA evaluates the economic, organizational, social, and ethical issues of health technology to inform policy creation. Drugs, medical devices, and medical products and procedures are all types of health technology.

For this paper, the focus is on HTA bodies responsible for assessing drugs.

Examples of HTA bodies tasked with drug assessments are the National Institute of Health and Care Excellence (NICE) in the U.K., the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, and the Agenzia Italiana del Farmaco (AIFA) in Italy. In many European countries, a formal HTA is needed before government payers will decide to reimburse a drug and push for its widespread use.

Relevance of RWE to HTA agencies

The weaknesses of RCTs are where RWE's utility is particularly evident. Jens Grueger, PhD, Affiliate Professor at the University of Washington, former Head of Global Access at Roche, and President-elect of ISPOR notes, "Real-world evidence is not a substitute for a well-conducted controlled trial, but there are many situations where you cannot do a well-controlled trial. In those situations, you really want RWE to complement your clinical data, for example, through external control arms."

Real-World Data and Real-World Evidence

According to the Food and Drug Administration (FDA) (2019), real-world data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources including electronic health records, claims and billing activities, product and disease registries, patient-generated data including in home-use settings and data gathered from other sources that can inform on health status, such as mobile devices.

The FDA also defines RWE as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analyses of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomized trials, including large simple trials, pragmatic trials, and observational studies.

There are three key areas for RWE use: innovating clinical development, accelerating access, and improving clinical practice.

RWE is already being used in several ways to improve patient care and delivery. A 2018 report by McKinsey and Co reveals that pharmaceutical companies have rapidly expanded their use of RWE from just safety and post-market. The report states that the years 2011 to 2015 "saw more integrated use of RWE across the end-to-end product lifecycle during which it was deployed to support regulatory decisions, advance disease understanding and clinical guidelines, and support outcome-based reimbursement decisions."

Looking from the perspective of HTA agencies' functions, RWE is better suited to the following investigations, contexts, and purposes:

GENERALIZABILITY

RCTs are difficult to generalize to clinical practice because of enrolment restrictions, budget constraints, study design limitations, difficulty recruiting sample population truly representative of the target population, and unduly controlled environments. With RWE, HTAs can evaluate the effectiveness of drugs on a wider range of patients with comorbidities and other variables not accounted for in RCTs— getting a clearer picture of the external validity of the study results.

UNDERSTANDING LOCAL CLINICAL PATHWAYS

RWE, unlike RCT, can provide up-to-date insight into how clinical pathways are being utilized in routine clinical practice. Care pathways can affect the effectiveness of drugs and other health technologies. For example, a drug will likely have differing levels of effectiveness if it is used as first-line therapy compared to second-line therapy. HTAs need RWE to assess how new drugs will fare in existing pathways or if drugs that are already part of such pathways need to be reviewed/reassessed.

CONTINUITY

RWE gives HTA agencies access to long-term effectiveness data which is essential to analyze the benefits and side effects of drugs for chronic conditions. The rising incidence of chronic conditions and the increasingly longer survival rates of patients with them also represents a huge and growing evidence gap for RWE to fill. In short, RCTs are delimited by time, and once they've been run, RWE is needed to validate their outcomes over time. RCTs are typically run with surrogate outcomes to ensure that effect can be measured in the time allotted for the study. However, RWE allows the evaluation of clinical endpoints—like survival—because there's the opportunity for more long term follow up.

EPIDEMIOLOGICAL STUDIES

RWE is essential to the acquisition of meaningfully accurate data on specific epidemiological investigations like incidence and prevalence of illnesses, unmet medical needs, patient population specifics, and burden of disease. This data is essential to HTAs in their formulation of informed recommendations on where and what healthcare spend is better directed towards.

COMPARATIVE EFFECTIVENESS

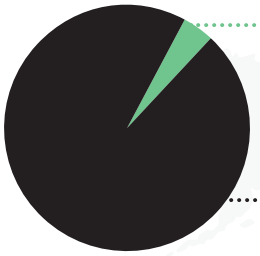
RCTs are undeniably useful in evaluating comparative efficacy, which is a prerequisite for regulatory approval. However, RCTs are deficient in evaluating comparative effectiveness as they typically exclude clinically relevant patient groups (e.g., children and pregnant women) and comparators commonly used in clinical practice. Using RWE can provide an accurate reflection of a drug's effectiveness in real-world clinical practice, which is more valuable for healthcare decision making.

PHARMACOVIGILANCE

RCTs are run in narrower populations making the detection of rare safety signals challenging. RWE allows for larger populations of patients to be studied, facilitating the detection of rarer safety signals. Carefully designed RWE studies can reveal trends in adverse drug events —information that is vital to HTA agencies and regulatory bodies during benefit-risk re-assessments/reviews of drugs.

The prevailing lack of use of RWE by HTA agencies

USE OF RWE BY HTAS 2012 - 2017[1]



4% discussed RWE in the assessment process

96% did not discuss or use RWE in the assessment process

Countries/markets examined **7**

Total HTAs examined **3,800**

HTAs that discussed RWE in assessment process **144**

"Some HTA agencies have recognized the difficult task of valuing drugs on limited RCT data and are willing to harness the utility of RWE to ensure they have the best evidence for decision-making. Doing this spans a wide spectrum of activity."

ASHLEY JAKSA
VP of Regulatory and HTA Products and Strategy at Aetion

USE OF RWD ACROSS 52 MELANOMA REPORTS (2011-2016)[2]

54%
RWD used for relative effectiveness assessments, predominantly to measure prevalence

88%
RWD was included in 88% of the reports that contained cost-effectiveness assessments

Current research shows that HTA agencies' use of RWE is low. One study examined over 3,800 health technology assessments carried out by HTA agencies in 7 different countries/markets between 2012 - 2017. It found that only 144 (4%) discussed RWE in the assessment process. RWE was overwhelming used to fill evidence gaps by supporting efficacy, usage, safety, economic modeling, and long-term efficacy, and not as a key influencer in decisions. (Jao & Jaksa, 2017).

Another study revealed that, in 2015, non-RCT data was used in just 10% of Canadian Agency for Drugs and Technologies in Health (CADTH) assessments, 20% of Pharmaceutical Benefits Advisory Committee (PBAC) assessments, and 36% of National Institute for Health and Care Excellence (NICE) assessments. Even more, no non-RCT data was used in any of the Institute for Quality and Efficiency in Health Care (IQWiG) assessments (Griffiths & Vadlamudi, 2016).

Finally, even in instances when RWE is considered, it is more often for cost-effectiveness evaluations than for comparative effectiveness. A study of 52 HTA reports on melanoma drugs found that RWD was included in 54% of the relative effectiveness assessments. Even then, it was predominantly to measure prevalence. However, RWD was included in 88% of the reports that contained cost-effectiveness assessments (Makady, et al., 2018).

USE OF NON-RCT DATA IN 2015

10%
Canadian Agency for Drugs and Technologies in Health (CADTH) assessments

20%
Pharmaceutical Benefits Advisory Committee (PBAC) assessments

36%
National Institute for Health and Care Excellence (NICE) assessments.

0%
Institute for Quality and Efficiency in Health Care (IQWiG) assessments

Griffiths E, Vadlamudi N. Not ready for the real world? The role of non-RCT evidence in health technology assessment. Value in Health. 2016;19(3):A286. doi:10.1016/j.jval.2016.03.760

EVIDENCE HIERARCHY OF CLINICAL STUDIES[3]

1 **Systematic reviews and meta-analysis**

2 **Randomized controlled trials**

3 **Controlled cohort studies**

4 **Uncontrolled cohort studies, single arm trials** (noncomparative studies/RWE)

5 **Case series and case reports** (noncomparative studies/RWE)

6 **Expert opinion, editorials**

7 **Unpublished sources**

Reasons for the lack of use

Evidence hierarchy
RCT is seen—almost universally among HTA agencies and other healthcare stakeholders— as the gold standard. While RCTs are important, they are not relevant for all hypothesis testing. This view relegates RWE to the status of a less important data source and less relevant for decision-making (Griffiths et al., 2017). However, this view is starting to change."With the quality of RWD we have now, we can generate regulatory-grade evidence that is suitable for use in decision making. We are going beyond just exploratory and descriptive analyses, and can now go further into understanding causality," Grueger says.

Unfamiliarity with RWE collection and generation processes
The workforces of HTA agencies are currently not comprised of personnel who have substantial experience with observational and non-randomized study designs and can expertly assess and evaluate RWE, or critique its sources. (Oortwijn et al., 2019).

Data quality and methodology distrust
HTA agencies' concerns about the trustworthiness of RWE generated by biopharma manufacturers impede its adoption in their assessment processes. As Grueger

noted, "A big underlying issue is credibility and trust. HTA agencies are concerned that the industry is manipulating the data, and so absolute transparency and a very practical approach to RWE generation is necessary."

Data challenges

There are a number of data challenges to generating high-quality RWE that hinder its use. For example, existing infrastructure incompatibilities limit the linkage of RWD across multiple sources. In essence, this makes it difficult to develop a wide look at the patient experience and capture important confounders and outcomes—all needed for high-quality evidence.

Managing access to data from EHRs and registries in line with policies and individual national laws like the European General Data Protection Regulation (GDPR), is another obstacle stakeholders have to overcome. It is essential that patient privacy is protected, but this is difficult, especially with rare diseases where the patient population is tiny and anonymization of data may be practically impossible.

The shift

Despite these challenges and barriers, HTA agencies are increasingly embracing RWE as an essential source of additional evidence, beyond the RCTs, to support their recommendations.

"Some HTA agencies have recognized the difficult task of valuing drugs on limited RCT data and are willing to harness the utility of RWE to ensure they have the best evidence for decision-making. Doing this spans a wide spectrum of activity," Ashley Jaksa, VP of Regulatory and HTA Products and Strategy at Aetion, says. "On one hand, we have HTA agencies that are looking to generate their own RWE for use in their assessments. And on the other, those that are starting to explore methodology for use—all of which is very promising."

Some HTAs are encouraging RWE submissions and the development of RWE throughout the entire drug's lifecycle. For instance, the HTA organizations in Canada, along with Health Canada, has developed principles to "guide the generation of RWE that would be consistent with the regulatory standard of evidence in place in Canada and internationally." These principles support the recent announcement that Health Canada is collaborating with CADTH to optimize the use of RWE in its regulatory decision-making. Similarly, NICE is actively exploring how it will "use broader sources of data [e.g., RWD] and analytic methods to enhance our existing methods and processes."

"The HTA agencies in the U.K., Australia, and Canada have relied on modeling for cost-effectiveness analysis for a long time. And so, for them, incorporating real-world data in their assessments is more straightforward," Grueger, says on why some HTA agencies are quicker than others to embrace the use of RWE.

Many initiatives are also working to standardize RWD collection methods, create policies centered around quality control, and generally increase the visibility of RWE.

Impact HTA is a project that's developing and disseminating methodologies and processes in areas like RWE (among others) with the overarching goal of enhancing HTA agencies. Impact HTA also aims to develop and disseminate tools to make collaboration between European member state governments, HTA agencies, and other stakeholders possible.

Another is the Massachusetts Institute of Technology's (MIT) NEWDIGS WISDOM project. This initiative is geared towards shedding light on how novel types of evidence like RWE, when integrated with RCT data, can impact decisions on biomedical product licensing, access, and use. NEWDIGS WISDOM additionally plans to create a structured framework for the planning and production of consolidated evidence (from RCTs and RWE) across products' entire life cycles.

Also noteworthy is the GetReal initiative whose ultimate goal is to "to drive the adoption of tools, methodologies and best practices from IMI GetReal* and increase the quality of RWE generation in medicines development and regulatory/HTA processes across Europe."

* IMI Get real project was a three-year collaboration between industry stakeholders, pharmaceutical companies, academia, HTA agencies and regulators completed in 2017

Preparing for increasing adoption of RWE

How biopharma can prepare

Build infrastructure to facilitate the identification, collection and analysis of RWD

Incorporate RWE in the brand's strategic plan by incorporating RWE generation throughout the product lifecycle

Engage early with regulators and HTAs on RWE development plans and how RWE will be leveraged to supplement RCT evidence in submissions.

Implications for biopharma

HTAs and regulators have shown strong interest in expanding the use cases of RWE and are committed to improving their assessment process by incorporating additional evidence beyond RCTs. In view of this increasing reliance on RWE, biopharma should be committed to:

Building infrastructure to facilitate the identification, collection, and analysis of RWD that is fit for purpose and is generated in line with guidelines for quality RWE development. "Innovative biopharma is thinking holistically about how RWE can be integrated throughout the drug lifecycle. An integrated infrastructure that is committed to principled database epidemiology will be a necessity to meet the evolving needs of regulators and HTA agencies," Jaksa confirms.

Incorporating RWE in the brand's strategic plan by incorporating RWE generation throughout the product lifecycle to use in support of internal decision making (e.g., RCT feasibility), and applications for regulatory and reimbursement approval.

Engage early with regulators and HTAs on RWE development plans and how RWE will be leveraged to supplement RCT evidence in submissions. This will increase transparency and trust in the RWE. Much like how multi-stakeholder dialogue currently informs RCT study design and submission, it must also be used to set RWE requirements, expectations, and standards for use in decision-making.

"Although real-world scientists can be found in many development teams, the decision-makers in biopharma still have limited experience with RWE. Fortunately, this is changing. Top-down, the heads of development are asking important questions about RWE, and bottom-up, the data scientists are helping them understand it," Grueger says.

He continues, "Decision-makers are no longer avoiding RWE in a bid to minimize risks during market access and HTA applications. Slowly, they are realizing that risk minimization is very costly and doesn't serve the ultimate goal of getting more drugs to patients faster. And that being able to do things faster and a little bit cheaper gives them an advantage."

References

[1] Miksad R, Abernethy A. Harnessing the Power of Real-World Evidence (RWE): A Checklist to Ensure Regulatory-Grade Data Quality. Clinical Pharmacology & Therapeutics. 2017;103(2):202-205. doi:10.1002/cpt.946

[2] Jao and Jaska 2018

3 Akobeng AK. Understanding randomised controlled trials. Arch Dis Child 2005;90:840–4.

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