

PUBLIC POLICY STATEMENT

REAL WORLD EVIDENCE: STANDARDS FOR SCIENTIFIC EXCELLENCE AND PUBLIC TRUST IN SCIENTIFIC DECISION MAKING

Real-world evidence is bringing new insights about the value and effectiveness of healthcare products and clinical pathways. Agreed quality standards based on established scientific practice are needed to ensure decisions that affect patient access to new medicines, quality of care and health system efficiency are informed by the best available evidence.

The growing availability of real-world data holds exciting potential for understanding the clinical and economic impact of new health technologies (which in this paper refers to innovative medicines and vaccines), and their effect on healthcare quality, health system efficiency and ultimately patients. While randomized clinical trials (RCTs) remain the primary source of scientific evidence regarding the safety and efficacy (performance under ideal conditions¹) of medicines and vaccines, healthcare decision makers around the world are increasingly interested in the potential of evidence that demonstrates how new medicines will perform in a real-world setting.

The COVID-19 pandemic and the search for effective treatments has highlighted both the importance of real-world evidence to provide valuable rapid insights to policymakers, payers and providers. In order to leverage the power of real-world evidence and the underlying data on which it is based -- and build healthcare decision makers' trust in using it, common agreed methods, quality standards and guidelines are needed.

What is RWE? Key Concepts

The explosion of digital healthcare data that has catalyzed the use of real-world data and real-world evidence is relatively new in healthcare decision making by regulators, HTA bodies and payers², and a common understanding of key concepts is still evolving across stakeholders and jurisdictions. The following definitions are well accepted:

- **Real world data (RWD)** refers to data relating to patient health status and/or the delivery of

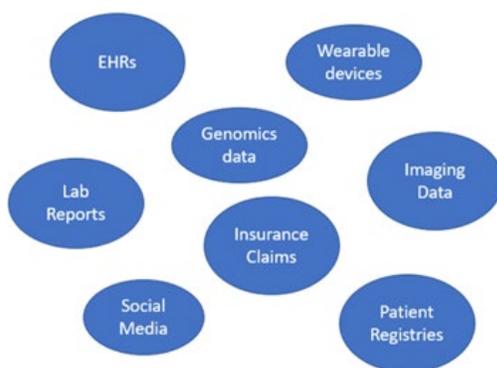
¹ Last, JM, ed. A Dictionary of Epidemiology, 4th Edition. New York: Oxford University Press, Dec 2000. ISBN-13: 978-0195141696.

² Rudrapatna VA, Butte AJ. Opportunities and challenges in using real-world data for health care. J Clin Invest. 2020 Feb 3;130(2):565-574. doi: 10.1172/JCI129197. PMID: 32011317; PMCID: PMC6994109.

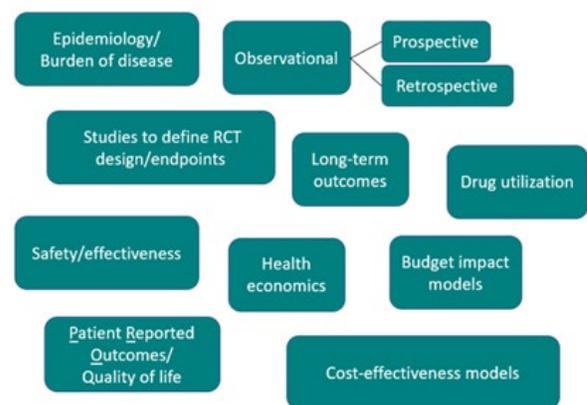
health care that is routinely collected from a variety of sources³, primarily outside the typical research (RCT) setting. Examples include insurance claims data, electronic medical records, prescription refill data, lab reports, physician notes, biomarkers and genomics data, patient registries, patient surveys, data from patient wearable devices, and social media data.

- **Real-world evidence (RWE)** refers to clinical or economic evidence regarding the use and/or potential benefits or risks of a particular health technology based on the analysis of RWD. RWE is usually generated in the form of a study using RWD to develop insights and inform healthcare decision making.
- **Observational studies** are a type of RWE that analyze RWD that has already been generated (retrospective) or is collected for study in the future (prospective). They answer specific, pre-determined scientific questions, typically regarding the utilization patterns, clinical or cost effectiveness of a medicine or vaccine. They are often non-interventional – meaning they do not involve active administration of a medicine or vaccine to participants.
- **Health economic models** utilize both clinical data sourced from RCTs, RWD and economic information. Such models provide estimates of the expected health or economic impact that may be achieved by adopting a specific health technology relative to its clinical comparators. These calculations include expected costs and financial consequences to the payer adopting a health technology (budget impact), as well as the projected value the technology (cost-effectiveness). Models are often used by policy makers, payers and health technology assessment bodies as one of several factors in estimating the value of a medicine or vaccine and in making decisions about healthcare resource allocation.

Potential Sources of Real-World Data



Potential Types of Real-World Evidence Studies



³ Framework for FDA’s Real-World Evidence Program, December 2018. <https://www.fda.gov/media/120060/download>

RWD and RWE: Critical support for 21st century decision making

RWE can help fill critical evidence gaps that cannot be addressed by traditional clinical trials, and may better reflect broad and diverse patient populations where products are used in clinical practice.

RWE is not a replacement for evidence from RCTs, which remain the gold standard for the assessment of efficacy and safety of a health technology. As an adjunct to RCT evidence, RWE can provide contextual insights that are not possible in a controlled setting, enabling better understanding of health technology use and impact in various patient subgroups that occur in the clinical practice setting. It also can be used to determine if RCT findings extend to clinical practice, and can inform the direction and design of future RCTs to facilitate additional investigation.⁴ RWE also can provide evidence for evaluating treatments where RCTs are infeasible, such as in the case of rare diseases.

For regulators, RWE offers expanded opportunities to review product evidence. Regulators may use RWE to update an existing product approval with new information on safety and effectiveness, to approve a new or expanded indication (such as a new patient sub-population) or a change in dosing regimen or routes of administration for an existing product, or in some cases to approve a new product for a rare disease. RWE may be used as a supplement to RCT evidence, or even in lieu of RCT evidence when RCTs are not feasible or ethical, as in the case of a rare serious condition with high unmet need. RWE may be used to gain insights into a product's long-term benefits or harms, or to assess product effectiveness through indirect comparisons.⁵

For payers and HTA bodies in particular, RWE can be particularly useful when reviewing the relative effectiveness of new treatments versus available standard of care, when analyzing the relative value of new products (cost-effectiveness, appropriate patient subpopulations or dosing regimen), and when re-assessing the relative effectiveness of treatments after they have been in use for a period of time. RWE also may be used to identify best practices to maximize the clinical utility of healthcare technologies or the quality of care. RWE is often used to answer questions about the budget impact of new medicines (uptake, duration of treatment, adherence/compliance rates); it can also improve understanding of the total cost of care and inform comparisons of the impact of new technologies on various parts of the healthcare system, such as hospital or outpatient care, or patients, caregivers, and family members.

Pharmaceutical researchers leverage RWD and RWE to better understand the natural history and burden of a disease, identify the prevalence of various outcomes and endpoints, and target research efforts accordingly. They also use it to identify appropriate patient subpopulations for inclusion in clinical trials, and to inform trial design and clinical development strategy. These insights can help ensure new technologies

⁴ O'Leary, CP and Cavender, MA. Emerging Opportunities to Harness Real-World Data: An introduction to data sources, concepts and applications. *Diabetes, Obesity and Metabolism*, 6 April 2020. <https://dom-pubs.onlinelibrary.wiley.com/doi/full/10.1111/dom.13948>

⁵ JC O'Donnell, et al. Evolving use of real-world evidence in the regulatory process: a focus on immune-oncology treatment and outcomes. *Future Oncology*, Published online 19 October 2020. <https://doi.org/10.2217/fon-2020-0591>

meet the unmet needs of patients and bring value to payers.

As individual health technologies move through the health system over time, the RWD generated by their use will be able to facilitate cross-functional learning among regulators, HTA bodies, payer and providers about the product's relative effectiveness vs. other available therapies in various patient types and under various clinical conditions. Studied over time, RWD and RWE will also improve our understanding of the effectiveness of approved care pathways and guidelines, the efficiency of payer resource allocation decisions, and health system performance versus patient needs.

Quality matters: Why clear standards for RWD and RWE are important

Meaningful quality standards are needed in order to build trust in RWE and ensure healthcare decisions are informed by the best available evidence.

While RWE can provide important insights into the safety, effectiveness and cost-effectiveness of health technologies, historically its application in healthcare decision making has been mostly limited to safety monitoring by regulatory agencies. Regulatory, HTA and other decision-making authorities are just beginning to develop guidance for how RWD and RWE should be assessed and utilized in addition to evidence from traditional RCTs. The US 21st Century Cures Act of 2016 required the FDA to explore greater use of RWE in decision making; since then the Agency has drafted a framework for the use of RWE and RWD, and health authorities in the EU, China, and others have issued similar documents on the subject.^{6,7,8,9} However, they are largely conceptual, covering the general circumstances of RWE use and procedures for submitting RWE. Unfortunately, these agencies have not specified 'fit for purpose' criteria for the quality or acceptance of RWE or its incorporation into current decision-making norms and processes.

Since RWE is a relatively new development in healthcare, many stakeholders have a degree of skepticism about its use. Common concerns include the absence of randomization in most RWE studies, the potential for studies to be influenced by biases and confounding factors that may be inherent in their design or the data they use, and the inability to ensure the quality of underlying data itself. In addition, there is a perception that some studies may be conducted without an a priori hypotheses – that is, they consist of data analyses that are performed without a clearly-formulated scientific question, and the decision to share the results is made after the results are known. Most are far more familiar with evidence generated by traditional RCTs, which are governed by well-known and internationally agreed standards of scientific rigor that both researchers and innovator companies are obliged to follow.

⁶ Food and Drug Administration (FDA). Framework for FDA's Real-World Evidence Program. December 2018.

<https://www.fda.gov/media/120060/download>

⁷ HMA-EMA Big Data Task Force. Phase II Report: Evolving Data-Driven Regulation. EMA/584203/2019.

https://www.ema.europa.eu/en/documents/other/hma-ema-joint-big-data-taskforce-phase-ii-report-evolving-data-driven-regulation_en.pdf

⁸ China National Medical Products Administration (NMPA). Real World Evidence for Clinical Trials in China. 16 Jan. 2020.

https://globalregulatorypartners.com/white_papers/real-world-evidence-for-clinical-trials-in-china/

⁹ Taiwan FDA. Taiwan Guideline for Basic Considerations for Real World Evidence for Drug Development.

Many do not realize that there are also significant standards of scientific rigor in the generation of RWE, many of which are modeled on existing standards for RCTs. Outcomes research experts are well aware of the challenges of conducting studies using RWD and the need to ensure studies that are appropriately designed and minimize bias and confounding. For this reason, professional societies such as the International Society of Pharmacoepidemiology (ISPE) and the International Society for Pharmaco-economic and Outcomes Research (ISPOR) have had long-standing guidelines for the generation of RWE.¹⁰ ISPE's guidelines for Good Pharmacoepidemiology Practice (GPP), last revised in 2015, are internationally recognized by both public and private researchers and other stakeholders as an important guidepost for ensuring the quality and integrity of evidence generated by pharmaceutical outcomes researchers. This list of essential practices includes:

- Use of pre-defined study protocols that contain:
 - A clear statement of research objectives, with a distinction between a priori hypotheses to be evaluated and hypotheses based on source data;
 - A description of the study design, sample population and selection criteria; data sources, methods of data collection, management and analysis; quality assurance procedures, and potential study limitations;
 - Plans for the protection of human subjects and their personal data;
 - Plans for dissemination and communication of study results;
- Verification that persons responsible for conducting the study are qualified to do so, and that research facilities are adequate to the task;
- Approval by an independent review body for any studies that involve human subjects;
- Recording of methods used to collect, manage and verify study data (while maintaining data security) in order to facilitate replication by others; and well documented and archived statistical analysis;
- Final report that includes the study objectives, methods, results, strengths and limitations – including circumstances that may have affected the integrity of the data -- and interpretation of study findings – including possible biases and limitations.
- Predetermined procedures for reporting and communicating studies; acknowledging an ethical obligation to report findings of potential scientific or public health significance, and legal obligation to report adverse drug events (as required by law);
- Secure archiving of study related materials, data and correspondence.¹¹

¹⁰ Berger, ML, et al. 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. *Value in Health*, 20:8, Sept 2017. <https://www.sciencedirect.com/science/article/pii/S1098301517333533?via%3Dihub>

¹¹ International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practice (GPP), 3rd Revision (2015). <https://www.pharmacoepi.org/resources/policies/guidelines->

populations, treatment practices, and willingness to pay thresholds. The most important consideration for assessing the appropriateness of using a specific study is whether it is fit for purpose -- valid and appropriate to answer the specific question the reviewer is asking.

- RWE studies that adhere to international standards of scientific rigor and are fit for purpose should be acceptable for consideration, regardless of the country in which the study was conducted, if it is sufficiently relevant to local conditions, including the relevant health system considerations.
- If RWE studies generated by third parties are considered in the decision-making process, those studies should be subject to the same standards of scientific rigor and use that have been applied to RWE supplied by originator companies.

Our actions

We adhere to rigorous scientific standards in RWD and RWE generation that are consistent with existing professional guidelines, and with our own scientific and ethical standards.

Merck's Center for Observational and Real-World Evidence (CORE) leads the Company's generation of real-world evidence research to significantly inform healthcare decisions and enable better access for patients. Reporting to Merck Research Laboratories, CORE is uniquely positioned within the company to generate scientifically robust information throughout the drug development and market lifecycle.

Our Company's RWE adheres to rigorous internal scientific standards that are similar to the processes we apply in our RCTs and are consistent with the aforementioned ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP), ISPOR and other professionally recognized organizations. Our standards of practice are based on a priori approach to research, including pre-specification of research questions and methods prior to hypotheses testing work. We perform rigorous scientific review of all study protocols and economic models to ensure that the research design is fit to answer the scientific question at hand. Our standards also demand that patient data is handled with respect for individual privacy/confidentiality and in concordance with legislative requirements, and that selection and remuneration to investigative partners is made in accordance with all legal and company compliance standards. A robust quality management system is in place to ensure execution of studies in line with Company and legal standards from concept development through publication. In order to ensure confidence in the scientific quality of our studies, decisions to publish product-related studies are made prior to initiation of the research activity.

Our company similarly follows rigorous standards of assessment to identify "fit for purpose" RWD sources to meet the RWE needs. RWD assessments are aimed at ensuring the delivery of high-quality, trustworthy (reliable), and analysis-ready data to support RWE studies. We use a multi-dimensional framework that includes assessments related to screening RWD sources (on population coverage, timeliness, use case experience, and data provider capabilities); evaluation of data elements (based on study-specific data elements and business rules specifications); evaluation of cohort identification strategies; as well as evaluation of internal and external validity of RWD sources. This framework-based approach enables

systematic examination of data sources to identify fit-for-purpose RWD for specific outcomes research needs. It also enables improved cross-stakeholder collaboration to improve the quality and reliability of RWD.

Our Company works closely with the external scientific and professional community as discussions evolve and toward a consensus on RWD and RWE quality standards and the role of RWE in various types of healthcare decision making. This includes the work of the American Medical Informatic Association (AMIA)¹², the European Bioinformatics Institute (EMBL-EBI)¹³ and TransCelerate BioPharma¹⁴ to identify and promote measures to ensure the quality and interoperability of available real-world datasets. CORE is also an active participant in efforts of the Duke Margolis Real-World Evidence Collaborative, the International Society of Pharmacoepidemiology (ISPE), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as they strive toward a shared understanding of RWE quality and the appropriate use of RWE in regulatory and health-technology assessment reviews. As these efforts continue, our Company will continue to provide its leadership and expertise to ensure future policies are informed by the scientific perspective of pharmaceutical outcomes researchers.

Conclusion

As health systems, the complexity of healthcare delivery, and new types of digital healthcare data continue to evolve and health technologies continue to advance, the need for new insights about the effectiveness and value of new products will continue to grow. Commonly agreed quality standards for RWD and RWE that are recognized by all healthcare decisionmakers will help build stakeholder trust in the evidence generated by innovator companies and ensure that decisions that affect patient access to new medicines, quality of care and health system efficiency are informed by the best available evidence. Our Company will continue to apply its high scientific and ethical standards to the generation of RWD and RWE in keeping with its tradition of breakthrough scientific research.

¹² <https://www.amia.org/amia2019/corporate-roundtable-registration>

¹³ <https://www.ebi.ac.uk/industry>

¹⁴ <https://www.transceleratebiopharmainc.com/initiatives/real-world-data/>