ISPOR SPEAKS

Transparency in Real-World Evidence: Trust, but Verify

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As healthcare decision-making complexity continues to intensify, health economics and outcomes research methods and experts have never been in higher demand. Innovative treatments with curative potential based on precision/personalized medicine have become a reality. The digital revolution is quickly coming to healthcare, including artificial intelligence algorithms aiding radiologists in diagnosing patients or augmented reality in the operating suite. However, these cutting-edge technologies complicate the value-determination process of patients, payers, and society, and accordingly, the healthcare budget-planning process. The increasingly complex innovative treatment options, combined with the growing focus on equity and access to healthcare, present a challenging combination of issues for decision makers.

In order to address these healthcare challenges, data are becoming the new "coin of the realm." While not a panacea, there is hope that understanding the nuances of healthcare delivery (ie, what is working and what isn't) will lead to a feedback loop of information that can make a functioning learning healthcare system a reality. Only by understanding what was done, why it was done, and the resultant outcome can we move closer to value-based healthcare.

There is growing interest in the use of "real-world" data (RWD) and their derivations into real-world evidence (RWE) to help inform healthcare decisions. With the advent of 21st Century Cures' mandate for the US Food and Drug Administration (FDA) to consider how to use RWE in regulatory decision making, RWD is expanding beyond signal detection and safety monitoring to contributing to treatment efficacy/effectiveness decision making. While payers may have been using postapproval observational data for coverage and reimbursement support and forward-looking single-payer systems and closed healthcare catchments like Kaiser Permanente are using RWE to drive improvements in healthcare delivery and quality, the regulatory use-cases are now driving RWE to a new plane in decision making.

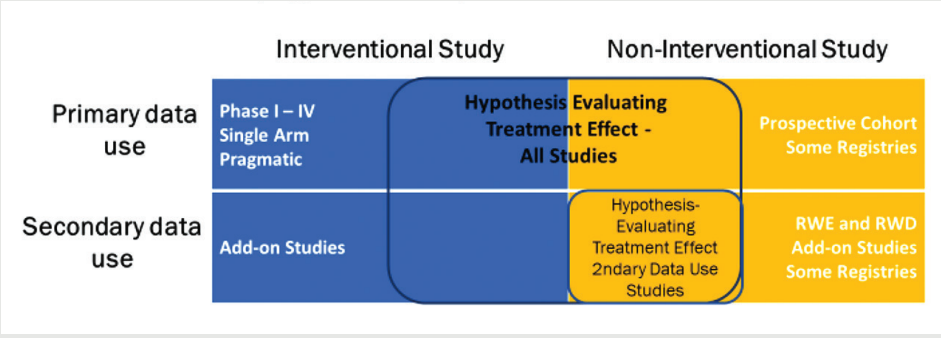
This creates urgency to develop mechanisms that promote trust in the evidence-generation process and enable decision makers to evaluate the quality of the methods and resulting evidence from RWE studies.[1-5] In other sectors such as government and consumer markets, transparency is a critical tool to engender trust across stakeholders and to enable the judgement of the quality of information being exchanged. It is intended to aid decision makers to set priorities and reach conclusions that are legitimate and fair—and perceived as such.[6] In evidence-based medicine, these needs are similar. Regulatory, coverage and reimbursement, and other healthcare decision makers need to be able to evaluate and make informed decisions based on high-quality, relevant evidence.

The need for increasing credibility in RWE is becoming more important as studies are being performed for purposes of informing healthcare decisions with more acceptance and impact. This is especially relevant as access to underlying data is increasingly difficult due to distrusted data networks and privacy laws, and as more studies are being performed with multiple underlying databases or within the "black box" of a machine learning algorithm.

Study registration—particularly for hypothesis-evaluating treatment effectiveness (HETE) studies—has been proposed as an important mechanism for improving transparency and trust. However, existing study registries such as ENCePP/EU-PAS and ClinicalTrials.gov are either oriented toward studies involving primary data collection, such as (randomized) controlled trials or prospective observational studies, or they lack many of the features that should be incorporated in a study registry system designed to improve transparency and trust for studies performed on existing data, often referred to as secondary data use (Figure 1).[7]

Building on the heritage of ISPOR's joint task force on RWE with the International Society of Pharmacoepidemiology

Figure 1. Data Use and Study Type Relationship Schematic



(ISPE), which identified posting a HETE study protocol and analysis plan on a public study registration site prior to conducting the study analysis as a key recommendation,[8] ISPOR has been leading the transparency charge. With our other high touch partners—ISPE, the Duke-Margolis Center for Health Policy, and the National Pharmaceutical Council—we've produced a white paper discussing the need for and recommendations for building a culture of transparency in RWE development and reporting. This effort starts with recommendations to modify or create a study registry site that may be fit-for-purpose for secondary data-use studies focused on causal inference (eg, HETE studies).

Near term, identifying the most suitable location or repository option(s) for preregistration of HETE RWE studies, with special considerations for non-interventional research, is paramount. Using one of the existing platforms (specifically leveraging the experience, expertise, and resources already allocated to these programs) is the most expeditious path forward. While current registry sites are not perfect for this purpose, they are good enough for RWE researchers to begin using them now as other longer-term options are evaluated and defined, including the opportunity to build a new registry.

In the medium term, determinations on additional modifications needed and how workload is affected are key to ensuring long-term success. Efforts will begin in parallel to near-term actions to determine what variables and documents should be registered and when. The starting point is surveying RWE researchers on what they feel is needed, including options for an embargo process, and how we might streamline pain points. The initiative will also work with other external efforts to capitalize on related workstreams, such as those looking at structured reporting and protocol templates that can inform data collection elements needed in a registry site. Definitions of prelooking and wording around attestation will need to be created and evaluated, as well as user reports and key performance indicators. Pilot testing of the mock-up site with actual research projects will be the culmination of mid-term objectives.

The long-term intention is to make registration of certain HETE RWE studies routine in the same way that clinical trials are now registered. Specifically, this is seen to involve studies intended for regulatory, payer, or other healthcare decision making, including peer-reviewed publications. The benefit of routine registration is to get closer to a full understanding of the totality of planned and completed HETE RWE research.

Other considerations also have to be taken into account, including the understanding that transparency does not equal quality—it only allows the end users of the research the best possible chance at making their own determination about how relevant and robust the results may be to inform the question at hand. The idea of what constitutes an appropriate or inappropriate amount of prelooking at the dataset prior to study start will also need to be addressed. While our initial thinking is to be "nonjudgmental" in defining levels of prelooking—only requiring transparency about what was done and for what purpose—the practicalities of that thinking will need to be tested. Versioning of study documents, including protocols and analysis plans, will also need to be defined at least loosely: What amount of change would require an updated document? How many versions are too many? and Does timing of the version lead to suspect results? Finally, incentivizing use of the registry is something that we will have to bear in mind; often such efforts require some motivating factor in order to become standard practice. Whether it's requirement by decision making end users (eg, FDA, EMA [European Medicines Agency], journal editors, or health technology assessment bodies) or incentives (eg, faster-track publication or seal of approval), we need to make sure that the evaluators of these studies are closely aligned with this initiative.

We've encountered a groundswell of multistakeholder support for this effort to date through our comments on the white paper, at the ISPOR Scientific Summit in October in Baltimore, and in the sessions at the latest ISPOR European meeting in Copenhagen in November. While we continue to work on the details with our steering committee and partners, it seems clear that we need to pursue a path forward as expeditiously as possible, but only with the combined efforts of the affected stakeholders, researchers, and the end users. As the potential use of RWE to support decision making for market authorization, reimbursement, and clinical guideline development grows, the need to trust that evidence grows correspondingly. Improving the culture of transparency can help shine light on study practices so that these end users of the results are able to make a better determination about study quality for themselves. •

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