

# Real-World Evidence: What It Is and What It Can Tell Us According to the International Society for Pharmacoepidemiology (ISPE) Comparative Effectiveness Research (CER) Special Interest Group (SIG)

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**On December 8, 2016, the *New England Journal of Medicine* published a sounding board on Real World Evidence (RWE)<sup>1</sup> by the US Food and Drug Administration (FDA) leadership. While the value of RWE based on nonrandomized observational studies was appreciated, such as for hypothesis generating, safety, and measuring quality in healthcare delivery, the authors expressed concerns on the quality of data sources and the ability of methodologies to control for confounding. In response, we offer a few considerations regarding these concerns.**

## WHAT ARE THE CHALLENGES AND THE LIMITATIONS OF NONRANDOMIZED OBSERVATIONAL STUDIES? CAN THE ADVANCEMENT IN THE CURRENT METHODOLOGY OVERCOME THESE OBSTACLES?

Currently, our evidence-based decision making largely focuses on randomized controlled trial (RCT)-based "efficacy" studies rather than "effectiveness" studies. Non-randomized observational studies make up the bulk of evidence in the "real world." Although different types of RWE studies exist, the issues that we tend to address in this Commentary are about observational studies, primarily the use of healthcare longitudinal databases with health insurance claims or electronic medical records (EMRs).<sup>2</sup> These two types of databases are the most commonly used data sources to generate RWE evaluating the use of medications and their effectiveness and safety in clinical practice or studying an unmet need / disease burden.

Confounding, selection bias, and information bias constitute a major threat to the validity of nonrandomized observational studies. However, with appropriate newer study designs and advanced statistical analysis, such as appropriate use of propensity score methods, confounding or biases can often be eliminated or largely reduced. Incomplete data on key outcome measures, preexisting medical conditions/complications, or laboratory values from existing data sources can lead to skepticism on the quality and value of evidence based on those databases. Yet validation efforts, quality assurance programs, and sensitivity

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analysis can help improve or ensure the robustness of findings.

The past decade witnessed some breakthroughs in methodological advancement for nonrandomized observational studies. In some cases, well-done analysis with complex methodology of RWE could sometimes substitute or replicate the findings from RCTs<sup>2</sup>. Uptake of the new user and active comparator study designs<sup>3</sup> have also gone a long way in mitigating confounding, as well as other forms of bias common in observational studies. The use of multiple imputation with chained equations in combination with other analytic techniques have improved the way we deal with incomplete or missing data on important confounding variables.<sup>4,5</sup> With the application of propensity score methodology and analytic techniques specifically targeting big data, including machine learning, we are becoming much closer to the quality of evidence expected in the context of RCTs. Propensity score methodology can address measured confounding factors well, even in the setting of rare outcomes, whereas conventional RCTs may be of low power.<sup>6</sup> In the context of large datasets, predictive models with machine-learning techniques can guide in the appropriate selection of variables for the estimation of propensity scores. In certain settings, a high-dimensional propensity score methodology can generate valid effect estimates when benchmarked against results expected from randomized trials.<sup>7</sup> Sensitivity analyses can help researchers understand the robustness of results, just as such analyses play a role in RCTs. The choice of the study design and the selection of the data source should be directed by the scientific question of interest, and should consider whether an RCT is feasible and/or appropriate. In the context of a noninterventional observational study, researchers should consider a feasibility assessment to determine if a selected data source contains sufficient and reliable information on outcomes and important confounding variables to answer the specific research question of interest.

As our data collection systems evolve, the completeness and data quality of large longitudinal health insurance claims and EMR databases are being enhanced on an ongoing basis. With rapidly evolving technology supporting linkage across multiple

sources of information, e.g., claims, registries, EMRs, and biobanks, the ability to control for residual confounding is rapidly improving. Moreover, other available methods such as instrumental variable analysis may help in the context of unmeasured confounding if used appropriately.<sup>8</sup>

### **CAN NONRANDOMIZED OBSERVATIONAL STUDIES GENERATE HIGH-LEVEL QUALITY EVIDENCE FOR DECISION MAKING? DOES EVIDENCE QUALITY RELY ON RCTs ALONE?**

Well-designed and controlled RCTs are recognized as the "gold standard" to assess medication efficacy, whereas nonrandomized observational studies are often proposed as a substitute when RCTs are not available or not feasible. Blinding is an important methodologic feature of RCTs to minimize bias and maximize the validity of results, and can have an important impact on outcome ascertainment and postrandomization decisions. Typically, observational studies are not blinded, but certain aspects (outcome assessment or adjudication) can be blinded to reduce bias. However, the bias from lack of blinding is less pronounced for objective outcomes. The concerns regarding the quality of evidence from nonrandomized observational studies are largely attributable to the "nonrandomized" design; yet methodological advances can often address confounding. More attention (rather than on randomization and blinding) is warranted on limiting potential selection bias and on assessing whether the population and outcomes can be reliably defined for the specific scientific question in the selected data source.

Many systematic reviews have compared the evidence obtained from RCTs vs. nonrandomized studies, and shown little evidence for meaningful differences in effect estimates between nonrandomized studies and RCTs when the same research question was being addressed in the same population, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions.<sup>9</sup> Evaluation of several key questions could serve to inform when and how the findings from nonrandomized observational studies could substitute for that of RCTs.<sup>2</sup>

Evidence from nonrandomized observational studies and RCTs are complementary and additive to the overall body of evidence. Both types of studies should be critically appraised and used for decision making. The availability of RCTs should not make nonrandomized observational studies unnecessary, and vice versa. If both types of studies are available and answer the same question, they should all contribute to the body of evidence. Existing guidelines on the evaluation of the quality of evidence based on nonrandomized observational studies can assist in this regard. While RCTs will continue to generate high-quality evidence that will determine and guide our treatments, large nonrandomized observational studies are also powerful resources, especially in the area of comparative effectiveness research, and can help answer appropriate scientific questions.<sup>10</sup> A list of key guidelines that can be used to evaluate the quality of published nonrandomized observational studies where health insurance claims and EMR databases are used can be found in **Supplemental Table S1**.

Most recently, the ISPOR and the ISPE created the joint Task Force to make recommendations on nonrandomized observational studies regarding 1) transparency in the reporting of study methodology, and 2) reproducibility and replicability of findings. These documents highlight the importance of replicability across different data sources and different methods, and the importance of providing sufficient detail to allow such replication. Transparency and replicability would substantially increase our confidence in the validity of observational studies and can offer a trustworthy base for the expanded use of RWE in healthcare decision making.

### **WHAT IS OUR RECOMMENDATION REGARDING THE USE OF RWE FOR DECISION MAKING?**

The current paradigm of evidence hierarchy in evidence-based decision making needs to be reviewed. We believe the validity of evidence may not necessarily solely depend on whether it is generated by "randomized" or "nonrandomized" studies. Well-designed, well-executed, and well-reported nonrandomized observational studies are a critical component of the

overall body of evidence. A framework from the FDA with scientific considerations for study design, population identification, outcome ascertainment, reducing potential biases, and analysis could be helpful in encouraging researchers to apply best practices. The use of RWE based on such studies should be considered more broadly in various decision-making settings, including clinical practice, Health Technology Assessment (HTA), and regulatory and postmarketing lifecycle management. In an era of pay-for-value and adaptive pathway in formulary and reimbursement decision making, we recommend a paradigm shift from largely relying on idealized RCT evidence, which may fail to reflect the true value of the drug or medical device, to more realistic RWE supported by high-quality data and robust methodology where the strengths and limitations of the generated data can be acknowledged. Another important future step would be for academic institutions to develop, and funding agencies to support development of high-quality healthcare databases, and rigorous educational training and fellowship programs to foster next-generation researchers and leaders. Educational efforts should also be extended to other healthcare stakeholders, including clinicians, policy decisions makers, and industry, to guide the appropriate understanding and use of RWE.

We are encouraged by the FDA's effort to enhance the use of RWE in regulatory decision making, e.g., the recent draft guidance on RWE for medical devices. As RWE can be critical in the evaluation of both safety and effectiveness of medications, we appreciate that the FDA is taking further steps moving in this direction by developing a framework and draft guidance

(no later than the end of 2021) on how RWE can contribute to the assessment of safety and effectiveness in regulatory assessment, such as in the approval of new indications.

Additional Supporting Information may be found in the online version of this article.

#### DISCLAIMER

The views and recommendations expressed in this article are those of the authors and the Special Interest Group on Comparative Effectiveness Research and do not necessarily reflect those of the International Society for Pharmacoepidemiology (ISPE) and this article is not an ISPE document.

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