VIEWPOINT

Real-World Evidence and Real-World Data for Evaluating Drug Safety and Effectiveness

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For hundreds of years, the development of new medical treatments relied on "real-world" experience. Discoveries such as citrus fruit curing scurvy described in the 1700s or insulin as a treatment for diabetes in the 1920s long preceded the advent of the modern randomized clinical trial. What these diseases had in common was a reliable method of diagnosis, a predictable clinical course, and a large and obvious effect of the treatment.

In the late 1940s, the medical community began to adopt the use of randomized clinical designs for drug trials.[1] The recognition that anecdotal reports based on clinical practice observations were often misleading led to the nearly complete replacement of this "real-world evidence" (RWE) approach to evidence generated using the modern clinical trial model. Although moving medical science toward greater scientific rigor, this transformation simultaneously diminished the use (and minimized the value) of evidence generated from practice-based observations. Randomization and blinding became the gold standard for determining the effect of treatment. With strict protocol-specified definition of eligible patients, populations studied began to diverge from patients encountered in clinical practice. Patients with wider ranges of disease severity and age, taking a broader range of concomitant medications, and with more and varying comorbidities were not as well represented in clinical trials.

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By controlling for key sources of bias, assuring appropriately matched study groups, modern clinical trials support drawing strong causal inferences regarding the efficacy of treatments, and thereby contribute to the substantial evidence of effectiveness necessary for regulatory approval. On the other hand, such trials do have important limitations, including high costs, extensive resource requirements, and often long timelines. Restrictive enrollment criteria and the concentration of trial sites in certain health systems make it challenging for some patients to enroll, including those with comorbidities, especially if mobility or cognitive abilities are affected. Thus, the trial population may not reflect the larger population that will use the drug.

The increasing accessibility of digital health data, spurred in large part by the transition to electronic health records (EHRs), together with rising costs and recognized limitations of traditional trials, has renewed interest in the use of real-world data (RWD) to enhance the efficiency of research and bridge the evidentiary gap between clinical research and practice. RWD can be defined as data relating to patient health status or the delivery of health care routinely collected from a variety of sources, such as the EHR and administrative data.

Under the 21st Century Cures Act, the Food and Drug Administration is tasked with developing a program to evaluate the use of RWE to support approval of new indications for approved drugs or to satisfy postapproval study requirements.[2] RWE can be defined as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. A framework for this program will be published by the end of 2018.

The FDA routinely uses RWD to provide evidence about drug safety, drawing on claims and pharmacy data from more than 100 million individuals in its Sentinel System.[3] In addition, FDA regulations have long recognized that historical controls taken from practice settings can be used as reference groups in single intervention group treatment studies that provide substantial evidence of effectiveness, for example, when the course of the disease is predictable (eg, certain rare diseases and cancers), and the effect of the drug is substantial. For example, the accelerated approval of blinatumomab for Philadelphia chromosome–negative relapsed and refractory B-cell precursor acute lymphoblastic leukemia was based on a single-intervention group trial. The threshold response rate was compared with historical data from 694 comparable patients extracted from more than 2000 patient records from the European Union and US clinical study and treatment sites.[4]

The FDA is now focused on identifying additional areas in which RWD may be used to generate evidence of effectiveness. This will require both an assessment of the quality and suitability of underlying data that will be used, and the analytical methods to generate the evidence. Through Sentinel, the FDA has considerable experience with the use of claims data, but claims data will not capture many of the clinical end points used to support new indications for approved drugs. EHRs can provide more granular clinical data, including laboratory results, imaging, and clinical assessments; however, EHR data are often unstructured and at times inconsistent due to entry variations across providers and health systems. This is not surprising because EHR data are not presently generated with research goals in mind.

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To better understand how RWD can be used to inform regulatory questions, the FDA Oncology Center for Excellence has entered research collaborations with Flatiron Health, a company developing quality real-world oncology data, and CancerLinQ, the American Society of Clinical Oncology's big data initiative. The focus of both collaborations is to use RWD to understand the real-world use of new immunotherapies. These and other FDA projects are assessing the completeness, accuracy, and consistency of electronic health data and will ultimately inform the FDA's assessment of the fitness of these data for use in regulatory studies.

Determining the optimum analytic approach to generate RWE is an area of considerable debate. Even though the setting in which traditional trials are conducted may reduce their external validity, randomization remains the key tool to support robust causal inference. Applying this important scientific tool to the real-world environment may minimize confounding while allowing generation of data from populations most reflective of patients who will receive the drug if it is approved. Randomization implemented in the setting of clinical care may result in a broader inclusion of patients and facilitate observation of patients in their everyday clinical environment. Building on the model of large simple trials, randomized trials can be increasingly integrated into clinical practice. These trials may include "pragmatic" features[5] that seek to mimic implementation of an intervention in routine clinical practice. Integrating research into clinical settings may present new challenges involving clinician workflow and require additional training to ensure good clinical research practice.

To explore how randomized trials can be conducted in real-world settings, the FDA is supporting the first randomized clinical trial in Sentinel, which to date has only been used to assess safety. The IMPACT-Afib[6] trial will test an educational intervention to address the important public health problem of underuse of effective medications to reduce the risk of stroke in patients with atrial fibrillation, and it could serve as a proof of concept for future RWE trials.

The FDA recognizes the interest in harnessing RWD and observational methods to generate evidence of effectiveness. Large patient databases are particularly helpful to study rare events, especially when those events are easily identified and are specific to the disease. Using customized statistical methods, observational studies may have the potential to provide evidence to inform regulatory decision making. The FDA has relied on observational controls when the end points have been well defined and the clinical course of the disease is predictable and well understood. Further research is needed to determine when large data sets and statistical methods are sufficient to correct for systematic bias in sampling, ascertainment, or missing data that may arise in observational studies—a particular problem with retrospective studies in which less well-characterized patients limit adjustments for confounders. As a part of this effort, the FDA is funding a study to explore whether observational methods can be used to replicate the results of approximately 30 clinical trials designed to provide evidence about the effectiveness of a drug. This project will assist the FDA in understanding how observational methods can be applied to address questions involving drug effectiveness.

The efforts of the FDA should provide insights regarding potential uses of RWE for regulatory decisions, but are just one aspect of a larger challenge. If RWD and RWE are to be effectively leveraged for public health purposes, there will need to be shared learning and collaboration across clinicians, patients, health care systems, pharmaceutical companies, and regulators. Just as the commercial data partners in Sentinel see the value in pooling resources to answer critical safety questions, further collaborations will be needed to create high-quality interoperable networks of data that can be seamlessly leveraged for clinical and research purposes. In addition, if research is to fulfill its goal of being patient centric, it will be necessary to leverage technological advances, such as mobile health, to capture the patient experience beyond the clinical delivery system and establish a more comprehensive picture of how medical products function beyond the controlled confines of traditional randomized clinical trials.

ARTICLE INFORMATION

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