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PERSPECTIVE

Evidence Generation for Drugs and Biological Products isn't Magic or Myth

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Deciding that a drug or biological product is safe and effective involves the generation of compelling evidence. Beyond clinical reasoning or case reports, the randomized, controlled trial (RCT) emerged in the mid-20th century as the archetype methodology for evaluating new therapies. RCTs are still the dominant paradigm for regulatory decision-making on effectiveness, but approaches to evidence generation are evolving in terms of the design and conduct of RCTs as well as non-randomized approaches to causal inference.

BACKGROUND

When describing epidemiologic study designs, a simple dichotomy of "randomized trials vs. observational studies" obscures what is better characterized as a spectrum ranging from RCTs to externally controlled trials, to observational studies. In addition, interest in and use of real-world evidence (RWE) has gained traction, but skepticism exists as to whether such evidence is persuasive,[1] represented by the phrase "the magic of randomization vs. the myth of real-world evidence."[2] This Perspective highlights contemporary issues across the spectrum of evidence generation, with a focus on regulatory decision-making.

In seeking to improve the certainty of results or increase the efficiency of study conduct, methods for generating and interpreting medical evidence change over time. Among other factors, technological advances that provide electronic access to large volumes of detailed healthcare data ("big data") are being used to evaluate therapeutic effectiveness, with or without the conduct of an RCT—and the concept of real-world evidence (RWE) has emerged.[3] FDA's Framework for a RWE Program[4] defines real-world data (RWD) as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources"; RWE is "clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD" regardless of the type of study design. Of note, although RWD can be used for various purposes (such as to identify participants for proposed studies or analyses of drug utilization), the remainder of this Perspective focuses on drug-outcome associations.

Misconceptions regarding RWD and RWE have arisen.[5] One misconception is that these terms describe new entities, yet sources of data and types of study designs haven't fundamentally changed. What is new is electronic access to reliable and detailed data for research purposes, providing opportunities for exploring epidemiological and statistical methods in lieu of randomization. Another misconception is, as mentioned, that a simple dichotomy exists between RCTs and observational studies—but the defining feature of a clinical trial is the assignment of treatment according to a research protocol, and not all clinical trials are randomized (e.g., single-arm trials).

RANDOMIZED, CONTROLLED TRIALS

Although the cause-effect relationship of an intervention may be obvious enough that an RCT is unnecessary (e.g., marked tumor shrinkage after a chemotherapeutic drug is administered), the circumstances in which such inferences are justified are limited. In general, RCTs remain a mainstay in scenarios including when: diseases have a variable course; comorbidities, concomitant medications, or patient activities confound conclusions regarding drug-outcome associations; responses to treatment are heterogeneous; awareness of treatment assignment affects outcomes; or assessments of outcomes require use of clinical assessments that are not routinely used in clinical practice. Randomization is a critical tool to promote the balance of risks for a

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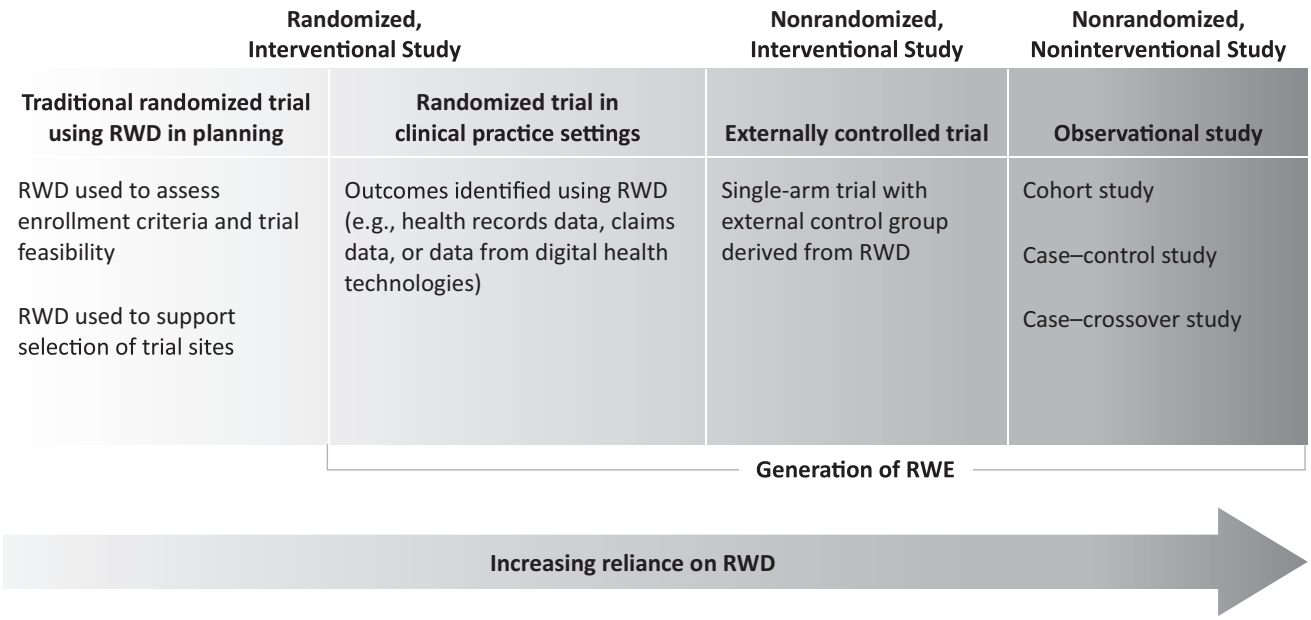

Figure 1 Spectrum of real-world data in representative clinical studies (adapted from *N Eng J Med* 2022; 386:1680). RWD, real-world data; RWE, real-world evidence.

given outcome across study arms—minimizing confounding due to differences in characteristics (e.g., comorbidity) that are associated with health outcomes.

Nonetheless, practical challenges for conducting traditional clinical trials exist, including for participants who face the burden of traveling to trial sites along with disruptions to their personal and work routines. In addition, advances in communication and information technology have revolutionized our ability to carry out many trial-related activities at patients' homes or other convenient locations. Telehealth, already a major part of patient care, is also valuable in clinical research and can make trials more inclusive and recruitment more efficient.

Recognizing these opportunities, the FDA recently finalized a guidance on trials with decentralized elements[6] which addresses strategies that can be used to bring trial-related activities to participants. These strategies include electronic informed consent programs, direct distribution of investigational products to patients' homes, telehealth visits with investigators, and the use of local healthcare providers and facilities to perform trial-related activities that are part of medical practice and require no research-specific expertise.

Technology is not only improving the convenience of trials but also has promise in improving the ways we measure responses to treatment. Miniaturized sensors can be worn or placed in the patient's environment to give rich, quantitative information on how patients respond to an intervention. Interactive applications on smartphones, tablets, and other electronic devices may facilitate the evaluation of interventions, often without the need for in-person assessments. These digital health technologies—if verified and validated to provide reliable data—can be used to make continuous or frequent measurements of movement, sleep, blood glucose, and other physiological features.[7] These technologies have the potential to detect rare clinical events (e.g., seizures, arrhythmias) and may allow us to measure physiological features (e.g., endurance, balance) in ways that were not formerly possible. With or without these advances, however, situations arise when RCTs cannot be done.

NON-RANDOMIZED STUDIES

"Non-randomized studies" to evaluate the effectiveness and safety of medical products refer to externally controlled trials (wherein outcomes in participants receiving the test treatment according to a trial protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment) and to non-interventional studies (wherein patients receive the marketed drug of interest during routine clinical practice and are not assigned to an intervention according to a protocol). Given that "observational" is used to describe various types of study designs as well as data sources, observational studies of drug-outcome associations can be described as "non-interventional" studies; see **Figure 1**. As mentioned previously, "RWD" and "RWE" have been added to the lexicon, in part attributable to the 21st Century Cures Act that included mandates for FDA to evaluate RWE.[5]

Multiple FDA centers and offices assess evidence generated from non-randomized studies, and FDA's RWE Program[8] for drugs and biological products serves as a hub for internal activities as well as for external engagements. For example, a multicenter committee promotes consistent decision-making, and public workshops and meetings have been held to seek diverse input on the use of RWE for regulatory decision-making. The RWE Program also supports research projects that can lead to improvements in RWE generation. An example is RCT-DUPLICATE, which sought to emulate the findings of RCTs using observational cohort analyses of RWD to assess the utility of these methods to support causal inference.[9]

FDA has also issued a series of guidance documents for the industry on aspects of RWE in regulatory decision-making for drugs and biological products. Topics

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Table 1 Representative challenges with non-randomized studies for regulatory decision-making

Real-world data sources:
· Issues with data reliability or relevance · Missing or "mistimed" data · Inadequate capture of endpoints · Need for linkage with other data sources
Design and interpretation of non-randomized studies:
· Residual confounding · Incorrectly specifying index dates ("zero time") · Inappropriate comparator intervention
Conduct of non-randomized studies:
· Protocol and analysis plan not pre-specified · Lack of access to patient-level data · Issues with conducting inspections

include evaluating sources of RWD (electronic health records and claims data; registry data), data standards, types of study design (point-of-care trials; externally controlled trials; non-interventional studies), regulatory considerations, and procedures for submitting applications with RWE.[8] This portfolio of recommendations provides sponsors and other interested parties with a tailored approach across a wide range of scenarios.

An underappreciated issue is that sources of RWD may not be suitable to assess a drug-outcome association; see Table. This observation should not be surprising, given that research priorities haven't historically been envisioned when data from routine clinical care are collected. Core considerations include data reliability (i.e., accuracy, completeness, traceability) and relevance (i.e., availability of data for key study variables, and sufficient, representative patients for the study). Specific concerns include missing data or data that are "mistimed" (in terms of being collected based on ad hoc clinical encounters rather than a protocol-driven schedule), insufficient capture of endpoint data, and the need for linkage with other data sources.

Even with reliable and relevant data, the design, analysis, and conduct of non-randomized studies involve complexities and challenges; see **Table 1**. Although details are beyond the scope of this overview, issues include residual confounding, incorrectly specifying index dates ("zero time") for the start of follow-up, and use of an inappropriate comparator. Problems with study conduct include protocols and analysis plans being developed or finalized as the evidence is being generated ("not pre-specified," such as external comparator groups selected when the results of the single-arm trial are already known). A challenge during regulatory review occurs when—for reasons such as data privacy—access to patient-level data isn't feasible.

Despite these challenges—and while maintaining FDA's evidentiary standards—the Agency is committed to realizing the full potential of fit-for-use RWD to generate trustworthy RWE. A landmark example involves Prograf (tacrolimus), approved originally to prevent organ rejection in patients receiving liver transplants, and later approved to prevent organ rejection for kidney and heart transplants based on randomized controlled trials. The drug had also been used routinely in clinical practice for patients receiving lung transplants, and FDA approved Prograf in 2021 for use in lung transplantation based on analyses of RWD from a transplant registry and confirmatory evidence of effectiveness from RCTs in other solid organ transplants.[10] This approval reflects how a well-designed, non-interventional study relying on fit-for-use RWD can be considered adequate and well-controlled under FDA regulations.

More recently, FDA has met two Prescription Drug User Fee Act commitments by launching an Advancing RWE Program[8] (that seeks to engage with sponsors early in their planning for a RWE study as part of their evidence package) and by publishing the first public report on RWE,[8] providing transparency on the contemporary use of RWE in regulatory decision-making.

SUMMARY

FDA applies existing evidentiary standards regardless of whether evaluating evidence generated from RCTs or non-randomized studies. The agency is promoting innovative approaches to the conduct of RCTs, and in parallel the Agency will continue to consider how non-randomized studies utilizing RWD can provide information to inform regulatory decision-making for drug effectiveness and safety. In conclusion, robust evidence generation is based on sound scientific principles, not on magic or myth.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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