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COMMENTARY

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Randomized, observational, interventional, and real-world—What's in a name?

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1 | INTRODUCTION

Epidemiologic study designs are the focus of renewed interest in the current era of real-world evidence (RWE).[1] Described with terms including case-control or cohort studies, observational designs were developed mainly to assess causes and correlates of human disease, but in recent decades, such methods have been used more frequently to evaluate the effects of medical products when used in routine clinical care (ie, not assigned by a research protocol), often with a focus on drug safety. Over the same time period, randomized controlled trials (RCTs) have become the archetype for experimental approaches (ie, protocol-assigned interventions). A dichotomy of randomized trials vs observational studies arose and was subsequently emphasized, related especially to the emergence of evidence-based medicine, with RCTs considered the benchmark of study designs—including for regulatory decisions that require adequate and well-controlled studies[2] as the basis for substantial evidence in support of the effectiveness of new drugs.

From a legislative perspective, the 21st Century Cures Act of 2016 provided specific milestones (see 21 U.S. Code § 355 g) for the Food and Drug Administration (FDA) to achieve in evaluating potential uses of RWE to support regulatory decision-making.[3] FDA has defined RWE as "clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data"[4] and real-world data (RWD) as "data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources."[4] (Of note, RWD differs from data collected in healthcare settings explicitly for research purposes.)

Contemporary discourse often invokes a choice between "randomized versus observational" and fails to articulate the spectrum of data and designs that can generate RWE. Without advocating a regulatory policy, this report considers terminology regarding RWE commonly used in the scientific community and seeks to reduce confusion when describing study designs.

2 | CORE ISSUE

As a prominent consideration, the distinction between a medical product assigned in an RCT and the same product provided as treatment during clinical care and assessed in an observational analysis is critically important in assessing causal inference for that product. Importantly, however, despite randomization being the key attribute leading to the ascendancy of RCTs, not all clinical trials with assigned treatments are randomized. Specifically, the defining feature of a clinical trial, whether randomized or not, is that the investigator assigns treatment according to an investigational protocol. Single-arm clinical trials assign an intervention to all enrolled participants without randomization, highlighting both distinctions within study design categories and the problem of adopting a binary randomized vs observational conceptualization.

3 | INTERVENTIONAL OR NONINTERVENTIONAL APPROACH

Focusing on the distinction between interventional and noninterventional studies—depending on whether the intervention (treatment) of interest is assigned according to an investigational protocol—can help researchers, sponsors, and regulators better understand and describe relevant methodological issues. A protocol-based investigation is noninterventional if the intervention of interest is given during routine clinical care, according to the clinician's judgment. Additional data collection from participants (such as questionnaires, imaging procedures, or laboratory tests) may invoke more stringent human subjects' protection, but if the investigational protocol does not dictate the patient's treatment, a study is still noninterventional from a methodological perspective.

4 | PRIMARY DATA COLLECTION OR SECONDARY DATA ANALYSIS

A second attribute of study design involves primary data collection for research purposes, secondary use of data obtained from clinical care, or both. Among interventional designs, traditional and decentralized RCTs involve primary data collected entirely or mainly from patients for research purposes. So-called pragmatic randomized trials[5] are often embedded within clinical practice and incorporate some secondary use of data collected as part of patients' routine clinical care, and cluster-randomized trials[5] use secondary data collected mostly or entirely from routine clinical care. Noninterventional studies often repurpose health record–based or claims-based data obtained from clinical practice—but observational design is not synonymous with secondary use of data. As one scenario, data collection when done according to a research protocol represents primary data even in a noninterventional context, and an observational analysis can then be used to generate results.

Considering the intervention and type of data together can promote better understanding of study designs when evaluating the validity of RWE to support effectiveness; see Figure 1. This

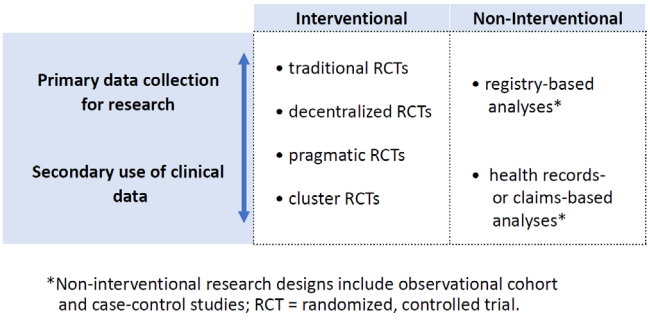

FIGURE 1 Examples of selected study designs classified according to intervention- and data-based axes. Of note, clinical trials with external controls (not shown) involve interventional arm(s) with primary data collection, as well as interventional or noninterventional comparison arm(s) that can include primary or secondary data [Colour figure can be viewed at wileyonlinelibrary.com]

KEY POINTS

- The U.S. Food and Drug Administration is evaluating potential uses of real-world evidence derived from real-world data in regulatory decision-making, but terms describing study design are often confusing.
- Although commonly invoked, a simple dichotomy of randomized trials vs observational studies is flawed conceptually.
- Important considerations include interventional or noninterventional study design and primary collection or secondary use of data; additional considerations involve attributes of comparison groups, assessment of causal determinism for the association of interest, and implications of the terms prospective or retrospective.
- Whether planning, conducting, or reporting research, clarity in terminology of study designs is needed.

conceptual framework was not as pertinent in the past when discussions of causal inference for therapeutic effectiveness involved mostly interventional studies with primary collection of data in traditional RCTs. Increasingly, however, and especially when only small populations are available or when ethical reasons exist for not randomizing, interventional studies are including comparison arm(s) using secondary data, as in externally[6] (or "historical") controlled trials. In addition, noninterventional studies involving primary data collection, such as registry-based analyzes, are also being done more frequently.

5 | ATTRIBUTES OF "CONTROL" (COMPARATOR) GROUPS

Importantly, cause-effect inference typically includes a comparison of some sort, and whether and how the study is "controlled" represent a related methodological consideration. Although RCTs use concurrent, randomly assigned controls from the same source population, other interventional studies use external controls (as mentioned) that originate from a different source population, lack concurrent timing, or both. For both interventional and noninterventional studies, characterizing relevant attributes of the study groups being contrasted is essential when assessing the validity of results.

6 | COUNTERFACTUALS—OR LEVEL OF CAUSAL (PROGNOSTIC) DETERMINISM

Another aspect of causal inference involves considering counterfactuals[7]—what outcome would have occurred without the intervention of interest—reflecting the level of causal or prognostic determinism attributed to an exposure-outcome association based

on available knowledge (such as confidence in understanding the underlying biology). In a simple example, given the counterfactual of what would happen after jumping from an airplane without a parachute, an RCT is not necessary to preclude chance or bias affecting the observed association between parachute use and a safe landing.[8] Extending this concept, prolonged survival after treatment with a new medicine among patients with a metastatic cancer that is uniformly fatal in the short term can be reasonably deterministic, given the expectation of virtually certain death, and an external control arm compared to an interventional arm could provide valid results. In contrast, cause-effect associations when assessing a subjective end point in a disease with a variable prognosis are much less deterministic, and to minimize bias, a randomized (concurrent) control group and other design features (eg, blinded assignment) would be preferable.

7 | IMPLICATIONS OF "PROSPECTIVE" OR "RETROSPECTIVE"

Finally, the terms prospective and retrospective alone do not completely characterize a type of study design. These labels have been used commonly, but variably, to indicate whether inferential reasoning is from cause-to-effect or vice versa, sample selection is based on exposure or outcome status, timing of the cause-effect association is prior to or concurrent with the investigation that is examining it, whether a study hypothesis is established prior to or after analyzing the corresponding data, or even whether study participants are reporting or recalling events (eg, exposure). For example, "retrospective study" can be used as shorthand for "case-control study" based on the directionality of inferential reasoning, whereas the potentially confusing phrase "prospective case-control study" describes a case-control structure with selection of case patients concurrent with study conduct. The potential for misunderstanding can be avoided by describing the underlying constructs involved (eg, retrospective cohort study design, with secondary use of data and sample selection based on exposure).

8 | ADDITIONAL COMMENTS

This *Commentary* focuses on terminology to help reduce confusion and promote efficiency when considering, generating, or reporting on RWE. Overly simplistic statements—such as "the replacement of randomized trials with nonrandomized observational analyzes is a false solution to the serious problem of ensuring that patients receive treatments that are both safe and effective"[9]—do not serve to advance the state of the science involved. At the same time, we acknowledge that the conceptual issues involved are more complex than described herein. For example, the distinction between RWD and research data is becoming blurred as clinical trials incorporate more data from routine practice settings and digital health technology ("wearables"), whereas disease and product registries are collecting data more systematically using formal methods.

A related issue, also beyond the scope of this paper, involves the fact that different design attributes can support valid inference in various regulatory contexts, and appropriate study design is best assessed on a case-by-case basis. In addition, we note that approval decisions by regulatory agencies (including the FDA[10]) have sometimes been based on nonrandomized evidence even before the 21st Century Cures Act was passed. Ongoing discussions, including this Commentary, can therefore be viewed as part of a continual effort to improve our understanding of assessments of causal inference by promoting clarity regarding related terminology.

9 | CONCLUSIONS

In the current era of RWE, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives. In this context, a "randomized trial versus observational study" dichotomy is overly simplistic as short hand for strength of study design to support causal inference. Clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s), as well as an assessment of prognostic determinism for the corresponding cause-effect association.

DISCLAIMER

This article represents the views of the authors and should not be construed to represent FDA's views or policies.

CONFLICT OF INTEREST

The authors declare that no conflicts of interest and ethical issues exist in relation to this work.

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