Annals of Internal Medicine

Deriving Real-World Insights From Real-World Data: Biostatistics to the Rescue

Michael J. Pencina, PhD; Frank W. Rockhold, PhD; and Ralph B. D'Agostino Sr., PhD

Randomized controlled trials (RCTs) are widely considered the gold standard for inference on the comparative effects of 2 or more treatment strategies. Randomization is the most powerful technique available in causal inference, and the controlled setting of carefully designed experiments is a necessity in evaluating most treatments. Still, as currently designed, conducted, and analyzed, clinical trials are not without limitations and might be susceptible to some of the biases present in observational studies (1, 2). Strict inclusion and exclusion criteria, as well as trials often being conducted "in parallel" with regular clinical care, have led to concerns that the enrolled sample might not adequately represent the population to which the tested intervention will be applied and that data collected during the trial, although generally of high quality, may not represent the "real world."

Another approach to obtaining evidence relies on *real-world data*, a term generally used to describe information collected as part of clinical care and everyday life. These data include electronic health records, registries, claims, and information collected through personal devices and apps. Although real-world appeal, ubiquity, increasing ease of access, and potential for lower cost make these data attractive for research, important limitations remain. Because the data collection process is not driven by research needs and does not follow what is routinely done in research studies, it may suffer from several shortcomings, including low interoperability between systems, excessive missingness, informed presence bias (3), and poor outcome ascertainment. Furthermore, studies conducted with real-world data are plagued by the use of inadequate and simplistic methods applied with the hope that the size of the data will compensate for the quality of the analysis.

Experts and regulators have called for tools and methods used in traditional trials to be adapted to real-world settings (4). Here, we describe 3 promising approaches: embedding RCTs within the universe of routinely collected health data, translating the results of an RCT to a population of interest, and applying modern comparative effectiveness methods to design experiments that mimic RCTs.

Embedding randomization within real-world data helps enlarge the trial-eligible population to make it more representative of the actual clinical setting (5). It is equally applicable to large, multisite trials and small, health system experiments. Given the relatively low cost of embedding randomization, it should be the default approach for testing new methods of care delivery. Embedding is illustrated by pragmatic studies, such as ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing the Benefits and Long-term Effectiveness) (6). This trial, which will enroll 15 000 participants, embedded randomization into electronic health record data from the National Patient-Centered Clinical Research Network (PCORnet) to determine the risk–benefit profile of 2 low doses of aspirin. Although most RCTs rely on simple, participant-level randomization, trials embedded in health systems and registries may benefit from cluster randomization at the site or provider level. This not only increases the feasibility and efficiency of the process but also builds in the appropriate hierarchy in which outcomes might be affected by site- or provider-related variability. Still, careful planning and execution are required to minimize the risks of imbalance and bias and to ensure appropriate handling of vulnerable populations.

If embedding is not feasible, another option may be to translate the results of an RCT to a population of interest. This may be done by fitting a model to the original trial data and then applying it to a sample from the target population. If sufficient heterogeneity exists within the original RCT and can be captured by using appropriate variables collected as part of the trial and also available in the target population sample, one may obtain more accurate results for the population of interest. This approach may be particularly relevant as we move toward value-based care, in which health systems will be interested in evaluating new treatment strategies based on the effect in their particular setting. Translating trial results to specific populations may be viewed as a step toward better precision of the results. True personalization may occur with the use of predictive models built to optimize trial results to individuals on the basis of benefit and risk considerations (7). The resulting treatment strategies must be validated in further studies, including RCTs.

Recent advances in comparative effectiveness research methods may help us design experiments that mimic RCTs. If appropriate data are available, such techniques as matching of fixed or time-varying variables in a longitudinal data setting, g-estimation, or parametric g-formula may be used to mimic the randomized setting reasonably well, provided that standard assumptions are met (8). Recent application of risk set matching over time allowed investigators to conclude that digoxin increases mortality risk in patients with atrial fibrillation. The study leveraged the existing data from a trial that randomly assigned patients with atrial fibrillation to receive apixaban or warfarin, with digoxin used concomitantly by some participants in each group (9). New propensity score–based techniques were proposed recently that put the weight where the equi-

This article was published at Annals.org on 24 July 2018.

poise is and achieve optimal balance on the measured covariates, and that better mimic what randomization does (10). These methodologies also may be used before a full clinical trial is designed for a new indication to inform the expected outcomes and to test the effectiveness of a treatment being used "off-label."

The differences in evidence from data collected as part of traditional clinical trials versus real-world data gathered as part of routine care create the false impression of dichotomy. Given the opportunities afforded by appropriate statistical methodology, moving away from RCTs as the sole view of clinical evidence is as important as expecting sufficient rigor and reproducibility from analyses performed on real-world data. Such trends as "open science," the push to open more clinical trial data to wider uses, and such efforts as PCORnet, which standardizes data collected through electronic health records across more than 100 health institutions, will accelerate this movement. Clinical research will benefit greatly from an acceptance that data are complementary, which will result in a much larger universe of health questions to be asked and answered.

From Duke University School of Medicine, Durham, North Carolina (M.J.P.); Duke Clinical Research Institute, Durham, North Carolina (F.W.R.); and Boston University, Boston, Massachusetts (R.B.D.).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-1093.

Corresponding Author: Michael J. Pencina, PhD, Duke University School of Medicine, 2400 Pratt Street, Duke Box 3850, Durham, NC 27710; e-mail, michael.pencina@duke.edu.

Current author addresses and author contributions are available at Annals.org.

Ann Intern Med. doi:10.7326/M18-1093

References

1. **Hernán MA, Hernández-Díaz S, Robins JM.** Randomized trials analyzed as observational studies. Ann Intern Med. 2013;159:560-2. [PMID: 24018844]
2. **Mansournia MA, Higgins JP, Sterne JA, Hernán MA.** Biases in randomized trials: a conversation between trialists and epidemiologists. Epidemiology. 2017;28:54-9. [PMID: 27748683]
3. **Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ.** Controlling for informed presence bias due to the number of health encounters in an electronic health record. Am J Epidemiol. 2016;184:847-55. [PMID: 27852603]
4. **Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, et al.** Real-world evidence—what is it and what can it tell us? N Engl J Med. 2016;375:2293-7. [PMID: 27959688]
5. **Lauer MS, D'Agostino RB Sr.** The randomized registry trial–the next disruptive technology in clinical research? N Engl J Med. 2013;369:1579-81. [PMID: 23991657] doi:10.1056/NEJMp1310102
6. **Jones WS, Roe MT, Antman EM, Pletcher MJ, Harrington RA, Rothman RL, et al.** The changing landscape of randomized clinical trials in cardiovascular disease. J Am Coll Cardiol. 2016;68:1898-1907. [PMID: 27765193] doi:10.1016/j.jacc.2016.07.781
7. **Pencina MJ, Peterson ED.** Moving from clinical trials to precision medicine: the role for predictive modeling [Editorial]. JAMA. 2016;315:1713-4. [PMID: 27115375] doi:10.1001/jama.2016.4839
8. **Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G.** Handling time varying confounding in observational research. BMJ. 2017;359:j4587. [PMID: 29038130] doi:10.1136/bmj.j4587
9. **Lopes RD, Rordorf R, De Ferrari GM, Leonardi S, Thomas L, Wojdyla DM, et al; ARISTOTLE Committees and Investigators.** Digoxin and mortality in patients with atrial fibrillation. J Am Coll Cardiol. 2018;71:1063-74. [PMID: 29519345] doi:10.1016/j.jacc.2017.12.060
10. **Li F, Morgan KL, Zaslavsky AM.** Balancing covariates via propensity score weighting. J Am Stat Assoc. 2017;113:390-400.

Current Author Addresses: Dr. Pencina: Duke University School of Medicine, 2400 Pratt Street, Duke Box 3850, Durham, NC 27710.
Dr. Rockhold: Duke Clinical Research Institute, 2400 Pratt Street, Duke Box 3850, Durham, NC 27710.
Dr. D'Agostino: Boston University, 111 Cummington Mall, Boston, MA 02215.

Author Contributions: Conception and design: M.J. Pencina, F.W. Rockhold, R.B. D'Agostino.
Analysis and interpretation of the data: M.J. Pencina, F.W. Rockhold, R.B. D'Agostino.
Drafting of the article: M.J. Pencina.
Critical revision for important intellectual content: F.W. Rockhold, R.B. D'Agostino.
Final approval of the article: M.J. Pencina, F.W. Rockhold, R.B. D'Agostino.
Statistical expertise: M.J. Pencina, F.W. Rockhold, R.B. D'Agostino.