

## VIEWPOINT

# The Imperative of Overcoming Barriers to the Conduct of Large, Simple Trials

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**Randomized clinical trials** remain the most reliable means of identifying the drugs, devices, and treatment strategies that will improve human health. There is increasing interest in the possibility that "personalized" medicine can be evaluated in much smaller trials because the average treatment effect is expected to be larger in highly selected cohorts. Smaller, biomarker-driven trials can provide major insights into whom to treat and may be sufficient for selected disease states in which considerable treatment effects may be observed. However, a precise biological understanding of most chronic illnesses and biomarkers that might predict response has eluded investigators. Moreover, treatment effect sizes in chronic conditions are expected to be modest in most cases. As a result, determining the long-term balance of risk and benefit, particularly in comparative effectiveness trials, often requires large numbers of clinical events in representative populations.

The conduct of large trials by government agencies, industry sponsors, academicians, and advocacy groups is limited by complexity and cost. As a result, many trials are too small to provide reliable estimates of the risk-benefit balance. Without adequate trials, clinicians will have insufficient guidance on how to meaningfully affect individual and population health. Achieving the "triple aim" (improving patient experience of care, improving health of populations, and reducing per-capita cost of health care) will require large, simple trials that efficiently determine the effect of interventions on clinically meaningful outcomes using adequate sample sizes at an affordable cost.

The Clinical Trials Transformation Initiative, a public-private partnership founded by the US Food and Drug Administration (FDA) and Duke University, convened a working group in May 2013 to identify barriers to the conduct of large, simple trials and opportunities to facilitate their use. The meeting participants agreed on 3 points.

First, trials determining the risk-benefit balance of therapies must be larger. Improvements in existing standards of care are likely to be incremental (10%-25% relative reduction in events), and large studies with numerous events are needed to identify moderate treatment effects. It is important that these trials use clinical, not surrogate, end points.

Second, trials must be simpler. The cost of large, complex trials—often hundreds of millions of dollars—is a significant hurdle, in both initially bringing a treatment to market and subsequently conducting comparative studies. Moreover, restrictive inclusion criteria and excessive exclusion criteria often limit clinicians' abilities to extrapolate findings to a broader, heterogeneous population. Data collection during the trial may

also be excessive, and this too adds to the cost. According to the Tufts Center for the Study of Drug Development, the typical clinical trial in 2012 involved 13 end points, 169 case report form pages, and 175 days of on-site monitoring.<sup>1</sup>

Third, for most therapies, studies must be randomized. Estimates of effect size in large observational studies may be precise but remain fundamentally hampered by bias and confounding that can be controlled only through random allocation.

Regulators have made substantial progress in promoting streamlining of large, simple trials. First, to help trial sponsors determine the amount and types of safety data that should be collected, the FDA issued a draft guidance in 2012 on "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations."<sup>2</sup> The intent of this guidance was to (1) improve the quality of safety assessment without compromising integrity and validity of trial results; (2) ease the burden on investigators and patients participating in a study; and (3) lower trial costs by facilitating the increased use of large, simple trials. Second, to improve the efficiency of monitoring while ensuring trial quality and subject safety, the FDA issued a draft guidance titled "Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring," which promotes strategies that can help sponsors focus on critical study parameters while reducing trial complexity.<sup>3</sup> Third, the FDA issued a new rule modifying investigational new drug safety reporting requirements for adverse events that must be reported within 15 days.<sup>4</sup> The rule focuses the reporting of unexpected serious adverse events to only those for which there is evidence to suggest a causal relationship between drug and event. Events common and anticipated in the population should be monitored and reported only if there is excess in the drug-treated group compared with the control group. Study end points should also not be reported as adverse events. Many sponsors follow the new rules, but overreporting persists, which is perhaps partly related to differences between US and non-US standards.

Despite interest from sponsors and support from regulators, adoption of large, simple trials remains limited. However, the case for improving the value of health care through more efficient clinical research is more compelling than ever. Contemporary priorities of funding agencies will encourage large and streamlined trials. The Patient-Centered Outcomes Research Institute is funding the development of interoperable research networks with databases that promote collaboration among patients, clinicians, health systems, and payers in large-scale and efficient research and should support the conduct of trials having larger sample sizes.

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Novel uses of existing data collection platforms present an opportunity to enhance patient enrollment in large, simple trials. Consenting patients can then be randomized with most of the necessary baseline history and laboratory data already recorded, minimizing data-collection needs. Quality-improvement registries, administrative claims, and electronic health records can minimize the need for additional data collection and onsite monitoring. The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial and Study of Access Site For Enhancement of Percutaneous Coronary Intervention for Women (SAFE-PCI for Women) are examples of randomized registry trials.<sup>5,6</sup> By leveraging the data collection abilities of existing registries, these trials can be conducted at a fraction of the cost of a conventional randomized trial. Initiatives such as the Health Care Systems Research Collaboratory will strengthen US capacity to conduct large and efficient research studies through networks of existing electronic health records and administrative claims data.<sup>7</sup> These research programs will establish infrastructures that enable health care systems to collaborate through shared data,

resources, and best practices while maintaining privacy and security safeguards.

Funding priorities and existing data collection platforms present a favorable environment for addressing important gaps in clinical evidence by facilitating large, simple trials. Accomplishing this will require researchers and clinicians to collaborate in a “learning health system” in which evidence is both generated and applied through the integration of research and care delivery. Pragmatically designed trials that operate in the context of routine clinical care can allow health professionals to collect data that help assess an intervention in representative care settings. To achieve a learning health system, trial sponsors, investigators, regulators, and patients need to share a common understanding of their obligation to encourage studies that will facilitate equitable and quality health care at a reasonable cost. Years of increasing complexity and cost in trials have created barriers to achieving such care. With the current opportunities to streamline trials and leverage existing clinical data, conducting large, simple trials is more possible than ever and presents a path forward for advancing human health.

#### ARTICLE INFORMATION

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