RANDOMIZED PRAGMATIC TRIALS: CAN THEY FULFILL THEIR PROMISE?

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Thoughtful collaborations between industry and academia can help PCTs gain acceptance as we seek more efficient ways to conduct studies.

The rising costs of clinical research and increasing investments required to bring new therapies to market are leading sponsors—private and public alike—to look for more efficient ways to conduct studies. In parallel, there is a growing call for clinical evidence that is relevant, timely, and meaningfully informs decision making for patients, providers, and payors. Regulators have proposed pathways that recognize the value of this data. Against this backdrop, pragmatic clinical trials (PCTs) are universally appealing: in general their ambition is to deliver easily implemented real-world studies that are better, faster, and cheaper than the randomized controlled trials (RCTs) that have historically formed the basis of clinical research. These goals can be accomplished in numerous ways, with a special focus on one or several of the attributes of a well-designed study, including: reductions in the amount and cost of baseline and outcome data being collected; lowering the costs of finding and enrolling patients; and reducing follow-up costs. These, and other strategies, make conducting a study more efficient by focusing on what is relevant for arriving at meaningful conclusions and safeguarding patient safety.

While the principles behind the conduct of a pragmatic clinical trial seem intuitive, their translation into real-world examples can be hampered by real or perceived barriers. Too often, trials originally designed as "pragmatic" expand to a full "bells and whistles," randomized controlled trial that loses its original nimbleness. This may happen for several reasons: traditional operational teams can drive the most pragmatic designs back to "standard procedures;" in other instances, researchers desire to answer more and more questions in a single study; meanwhile, the biggest hurdle can often be real or perceived regulatory requirements. Although the leaders of regulatory agencies have pushed for more pragmatic approaches, this message has not always been heard when decisions are taken regarding specific trials.

Equally, however, there are major factors facilitating more pragmatic approaches. The most significant of these may be the volume of data collected and made available for research. The nearly universal adoption of electronic health records (EHRs) in the United States creates unprecedented opportunities for pragmatic clinical trials. These clinical data offer the potential of better study planning, easier patient identification and recruitment, ready baseline data collection, and easier follow-up. Effective use of this data, nevertheless, requires a sophisticated understanding of hospitals' myriad and often complicated EHR systems.

Multiple PCTs have been successfully conducted, including the Salford Lung Study, MI FREEE[1], and the ongoing ADAPTABLE trial, which compares the risks and benefits of two different low-dose aspirin regimens for prevention of cardiovascular disease. ADAPTABLE is a PCT that draws from EHRs, Medicare claims, and patient reported outcomes.

1. Myocardial Infarction Free Rx Event and Economic Evaluation—this study found that enhanced prescription coverage improved medication adherence and rates of first major vascular events and decreased patient spending without increasing overall health costs; see http://www.nejm.org/doi/pdf/10.1056/nejmsa1107913.

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It is important to realize that ADAPTABLE has several features that make it ideal to be run as an EHR-based PCT, which many other types of trials may not satisfy. The drug being evaluated here is over-the-counter; therefore, safety reporting and drug distribution are simplified. Additionally, the outcomes measured in ADAPTABLE are "hard" (clinical events) and thus easy to verify in hospital records (that is, hospitalizations for myocardial infarction and stroke).

Another set of opportunities for PCTs lies in efficient trial design. The use of meaningful composite outcomes, "borrowing" of data from past experiments on the same population, different forms of trial adaptation, and early detection of unsuccessful treatment arms can all substantially decrease the number of patients that need to be randomized. Furthermore, limiting data collection to what is necessary, together with efficient interim monitoring that incorporates "quality by design," can result in better trials conducted for less money.

The most important step in enabling greater use of PCTs is a change of mindset. This needs to occur within the organizations sponsoring clinical research, among those responsible for conducting the research, as well as among the regulators—a few successful examples of modern PCTs will go a long way toward paving the road. Engaging with those who are not afraid to innovate is necessary to achieve meaningful progress.

Beginning the process of change will happen by ensuring that PCTs are aligned with questions that reflect clinical, economic, and policy priorities. Accordingly, ensuring that PCTs are well designed, built upon the correct data infrastructure, reflect meaningful clinical outcomes, and incorporate robust analytical capabilities will be necessary. This approach, particularly when framed in the context of strategic priorities, is rarely found within pharmaceutical manufacturers today.

Bridging this gap will require manufacturer, academic, and strategy collaborations that draw on each group's strengths. To that end, industry-sponsored PCTs should play an important role. By demonstrating that PCTs can be used to evaluate patented agents, these studies would begin to break down assumptions surrounding regulatory barriers to approval. PCTs can provide more tangible measures of effectiveness and assess the real-world outcomes that payors are increasingly requesting. Sponsors should not be afraid to invest in trial innovation and understand that this investment may not pay off in the first few applications: there is a learning curve to successful disruption and mistakes and inefficiencies will happen along the way. To navigate this process, our experience suggests that sponsors will benefit from guidance from thoughtful collaborations between academia and industry. Through an iterative process, these collaborations can provide guidance in understanding the role of PCTs, preparing for PCTs, and aligning PCTs with strategic priorities.

We are at an important junction in the history of clinical research where the role of PCTs is still being defined. PCTs cannot replace all RCTs for answering definitive questions around efficacy. Yet, with untenable costs, increasing demand for relevant evidence, and ample sources of new data, it is clear that PCTs have an important role to play. Thoughtful collaborations between industry and academia can provide the initiative and support needed to make this a reality.

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