

level playing field for all stakeholders. What is sometimes labeled as “free riding” may ultimately pay dividends for innovative companies and for public health. It is ironic that the organizations that most resist wider access to data are the ones that stand to benefit so much from greater transparency.

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The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

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Related article, p. 1587

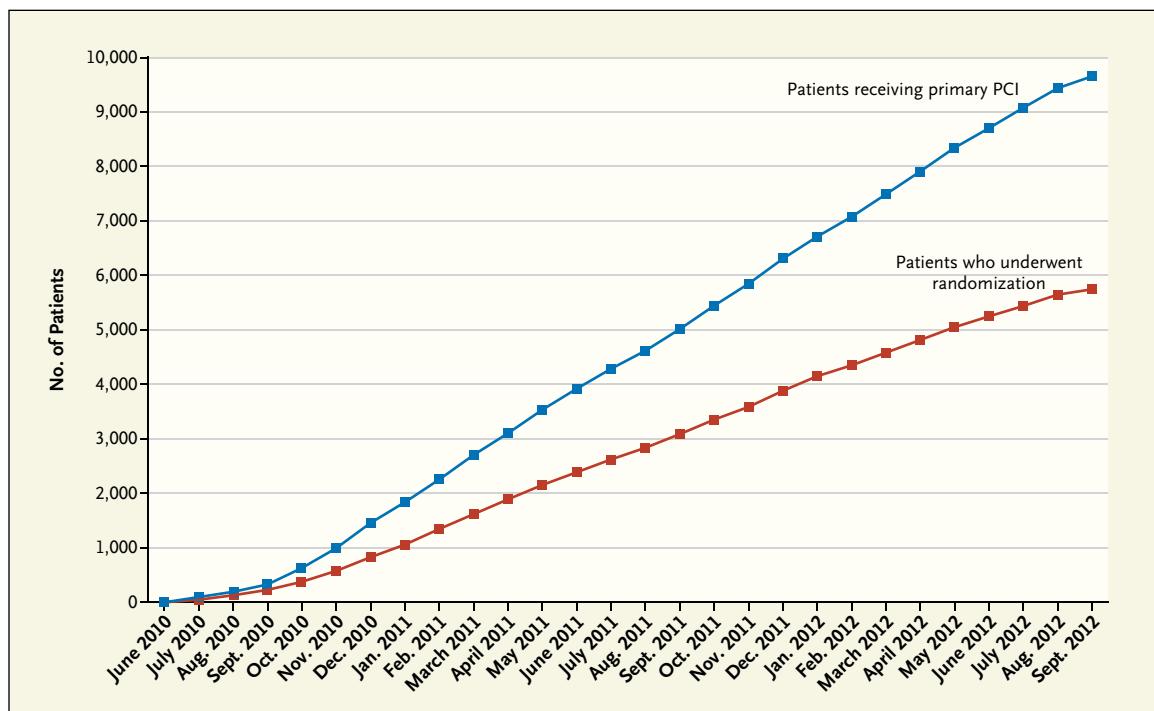
The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for the effects of unmeasured confounders and selection bias by indication. Randomized trials, especially huge megatrials, have transformed medical practice. Thanks to randomized trials, we no longer, for example, treat acute myocardial infarction with lidocaine and nitrates. Instead we use rapid revascularization, anticoagulants, and antiplatelet agents, and during long-term follow-up we routinely prescribe statins, beta-blockers, and angiotensin-converting-enzyme inhibitors. But the reputation of randomized trials has suffered of late,¹ owing to reasonable concern about excess complexity, expense, and time required to recruit study partici-

pants, as well as inadequate representativeness. What good are trials if the results aren’t applicable to real-world patients and if, because of excessive expense, they can be used to answer only a tiny fraction of our important clinical questions?

One possible solution is to look to observational registries for answers. Over the past 20 to 30 years, a number of professional societies, government agencies, private corporations, and independent researchers have established high-quality registries that collect standardized data from patients seen in a variety of settings. In cardiovascular medicine, for example, registries in the United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as from patients with rare diseases

such as hypertrophic cardiomyopathy and patients referred for surgery, percutaneous invasive procedures, and device implantation. Investigators and public health officials use registries to describe practice patterns and trends, to identify outliers, and to detect safety signals. They often use registries to assess comparative effectiveness, too, but are forced to admit that purely observational findings may not be internally valid owing to the absence of randomization.

As debates about comparative-effectiveness research have intensified over the past few years, we find ourselves in a kind of intellectual trap: yes, in theory we would like to conduct more randomized trials, but in practice they are too complex and difficult to apply to many clinical questions. And, yes, in theory we could answer many questions at



Rapid Randomization in the TASTE Trial, with Enrollment of Most Patients Receiving Primary Percutaneous Coronary Intervention (PCI).

Adapted from the Institute of Medicine (www.iom.edu/-/media/Files/Activity%20Files/Quality/VSRT/LST%20Workshop/Presentations/Granger.pdf). The incremental cost of the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial was \$300,000, or \$50 for each participant who underwent randomization.

low cost with large-scale observational registries, but despite statistical advances, comparative observational registry studies are suspect because they lack the rigor of randomization.²

Enter the registry-based randomized trial. With the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial, the results of which are now reported in the *Journal* (pages 1587–1597), a new paradigm has emerged that can potentially release us from the circular (and expensive) trap of the randomized-versus-registry debate.³ The TASTE investigators designed a large-scale trial to answer an important clinical question and carried it out at remarkably low cost by building on the platform of an already-existing high-quality observational registry. With

this clever design, which leveraged clinical information that was already being gathered for the registry and for other preexisting databases, the investigators were able to quickly identify potential participants, to enroll thousands of patients in little time (see figure), to avoid filling out long case-report forms, to obtain accurate follow-up with minimal effort, and to report their findings, all for less than the amount of a typical modular R01 grant (i.e., a grant for research initiated by an individual investigator) from the National Institutes of Health. Their findings may well be broadly generalizable, since they included in the randomization process the majority of all patients treated for ST-segment-elevation myocardial infarction in the study area.

The registry-based randomized

trial complements the strengths and addresses the weaknesses of the two most prominent types of comparative-effectiveness research. The trial is still a trial, a rigorous randomized experiment that isolates a causal link (or the absence of one) between a treatment and an outcome. Because the trial is inexpensive, investigators can enroll large numbers of patients, thus offering clinicians insights that are potentially based on a representative sample, a real-world population created from consecutively enrolled registry patients.

Despite this appeal, a number of fundamental questions must be addressed if we are to transform our clinical-research enterprise to give registry-based randomized trials, or other trials with highly efficient designs, a

prominent role. Will registry data (or data coming from other digital sources, such as electronic health records) be of high enough quality? Will too many data fields be missing? How will we balance efficacy versus effectiveness? Can we transition single registries from efficacy to effectiveness, making it possible to assess external validity much more expeditiously than we do now? What are the best populations or subpopulations to study? How will we approach concerns about privacy and informed consent (particularly in the context of trials that compare acceptable standards of care and use cluster-randomization methods)? Is blinding possible? Will researchers be able to obtain long-term follow-up or measure composite outcomes? How will we standardize and adjudicate certain outcomes? Can we assure representativeness, given that even within a registry there may be systematic differences between patients who are and are not eligible for randomization or between those who do or do not consent?

These are only some of the problems we will have to address. The TASTE trial was performed in Scandinavia, where the health care and information technology environments are markedly different from those elsewhere in the world. Can randomized registry trials be undertaken outside

Scandinavia, in places where health care and clinical data are fragmented and of lower quality? Some American investigators are already using the approach (e.g., the Study of Access Site for Enhancement of Percutaneous Coronary Intervention for Women; NCT01406236). But even if we can perform many more randomized registry trials in the United States, we must recognize that the approach cannot solve all the problems we have with trials. For certain kinds of trials, such as metabolic efficacy studies that focus on complex physiologic and metabolic pathways hypothesized to respond to changes in diet or to experimental pharmacologic agents, current organizational structures would probably work much better with only minor modifications.

The randomized registry trial represents a disruptive technology, a technology that transforms existing standards, procedures, and cost structures. Will it be given serious consideration as a way to resolve the recognized limitations of current clinical-trial design? Theodore Roosevelt once said, "Do what you can, with what you have, where you are." Today we can no longer afford to undertake randomized effectiveness trials that cost tens or hundreds of millions of dollars. But today we also have registries and other powerful digital platforms. Today it may

be possible to design and conduct megatrials with what we have: bigger data and smaller budgets. Yet we must also recognize and acknowledge the daunting challenges that diverse groups of researchers and stakeholders must overcome to get there.

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Smoothing the Way to High Quality, Safety, and Economy

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In recent years, health care institutions have awakened to the need to provide safe, high-quality care at lower cost. The Centers for Medicare and Medic-

aid Services is implementing multiple incentives and penalties intended to help realize this goal. For example, innovations designed to reduce the rate of in-

fections associated with ventilators or central venous catheters have had demonstrated success. We believe that greater attention to a frequently overlooked param-

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