In the TV game show *Family Feud* contestants are asked to fill in the blank for sentences or phrases, with the “right answers” coming from previously completed surveys. Some entries are easy, like “Don’t judge a book by its ______.” Others are less so, like “Prime ______.” If there were a medical version of *Family Feud*, an easy question, at least in contemporary times, would likely be “Expensive Clinical ______.” A more difficult, if not impossible, one would be “R____ R____ Trial.” What two juxtaposed “R words” would make sense?

Many have predicted the demise of the clinical trial. “Too expensive! Too limited in population, outcomes and intervention! Results are not generalizable to my patients.” However, even the naysayers agree that clinical trials yield the highest quality medical evidence. Practice guidelines cite results of large-scale clinical trials and well-conducted clinical trials can diametrically change medical practice.¹ Arguably, it would be better to change the way we conduct clinical trials than to discard the methodology. If we can make clinical trials cheaper, quicker, and relevant to more patients, they will continue to provide high quality evidence.² To get there, we will need to do research on the way we do research.

In the spirit of doing research on research, NHLBI officials recently took a hard look at the Institute’s clinical trial portfolio.³ Among 244 trials funded over a decade, less than 20% focused on clinical events. Yet those handful of trials accounted for over 80% of the citations and were published many times faster; indeed many of the small-sized surrogate endpoint trials were never published or only after a long delay. Commentators argued that these findings should offer impetus to funders to change their priorities, shifting focus towards large simple trials that focus on clinical endpoints.⁴

Meanwhile, some clinical investigators have begun to experiment with radically new methods with some success, as at least 3 recent high profile trials have utilized increasingly novel approaches of leveraging existing digital platforms to conduct high-impact, low-cost trials.⁵⁷ Others have experimented with large-scale cluster randomization.⁸ Yet trials that radically depart from “tried and true” methods remain few and far between; in the current tough research funding environment researchers are understandably conservative in their proposals. Catalysts are needed.

One catalyst is success: investigators apply disruptive approaches to important clinical questions and show “the rest of us” that their approaches work. In the March issue of the *American Heart Journal* Hofman and colleagues describe their plans for conducting a “registry-based clinical trial” that will assess the value of supplemental oxygen in patients with acute myocardial infarction.⁹ It is hard to believe that after so many decades we do not know whether this therapy is beneficial, neutral, or harmful. No private company stands to gain from a trial of supplemental oxygen, and budget-squeezed federal agencies may be reluctant to devote sizeable monies. Hofman’s group has already shown that it can conduct large-scale clinically relevant trials that employ existing registries as a platform. The “Thrombus Aspiration during ST-Elevation Myocardial Infarction Trial (or TASTE)”⁶⁷ randomized over 7000 patients and successfully completed an event-driven trial at an incremental cost of only $300,000.² We have every reason to believe that the currently planned trial on oxygen supplementation will yield a clinically interesting answer, one that will be published, disseminated, and included in guidelines, and yet one that, unlike most event-driven trials, will entail minimal marginal costs.

NHLBI seeks to offer another catalyst with targeted funding announcements, which set aside dedicated research dollars and assemble special grant-review groups. In 2012, the Institute issued the Request for Applications (RFA) “Pilot Studies to Develop and Test Novel, Low-Cost Methods for the Conduct of Clinical Trials” (HL-12-019). We challenged investigators to develop and test new methods that (1) minimize specialized study infrastructure, (2) minimize trial-related visits, (3) explore novel methods of obtaining informed consent, and 4) employ low-cost methods of monitoring study conduct. In November, 2013, NHLBI released a second RFA, “Low-Cost, Pragmatic, Patient-Centered Randomized Controlled Intervention Trials” (HL-14-019), which will use a two-phase cooperative agreement mechanism to plan, conduct, and support low-cost, pragmatic randomized controlled trials. We are seeking to support trials that will have high impact to patients or health care providers, and that leverage existing clinical practice settings and/or existing electronic resources.
such as registries for the conduct of clinical trials. Randomized registry trials would be highly responsive.

In these times of unprecedented fiscal austerity and rapid health care reform, we dare not throw out our strongest research method. Instead we should learn new, indeed disruptive, ways to conduct clinical trials that preserve their strengths while reducing cost and increasing generalizability. The randomized registry trial may well be a disruptive technology, a technology that upends and displaces existing paradigms.11

We have seen numerous examples in which mainstream establishments ignored, or even resisted, emerging disruptive technologies: think of the personal computer, digital photography, hydraulic lifts, and smart phones. Large organizations, be they corporations, universities, or government funding agencies, often find themselves stymied by their own business structures and values when faced with the prospect of fundamental shifts.11 Ironically, economic realities may nudge, even push, the research enterprise into adopting an approach that creates a learning health care system in which two R’s (randomized and registry) are juxtaposed and synergized into four (randomized, registry, representative, and really inexpensive). Medical Family Feud may be no longer be fun, but clinical research sure will be and all our patients will be better off for it.

References