Randomized controlled clinical trials (RCTs) are often held up as a touchstone for assessing the safety and efficacy of new drugs and vaccines. Because randomly assigning patients to either a control or intervention group renders the two groups comparable and reduces bias, RCTs have become the coin of the realm in drug and vaccine development. However, some people have argued that there are situations in which RCTs might prove not only too time-consuming or difficult to conduct, but unnecessary and unethical, such as with rare diseases that affect a vanishingly small group of patients and pandemic outbreaks that can affect entire communities. Patients with life-threatening conditions are often understandably desperate for treatments, lending a sense of urgency to the search for promising products and the hope that innovative trial designs might accelerate the development of cures. Luciana Borio, who has served as the US Food and Drug Administration’s (FDA) acting chief scientist, has garnered a wealth of experience in leading the agency’s response to an array of epidemics, including the 2009 H1N1 flu pandemic, the 2014 West African Ebola epidemic, and the ongoing Zika virus outbreak in the Americas. Borio’s efforts to coordinate clinical trials in epidemic settings have strengthened her conviction that RCTs continue to be the most rapid, reliable, and ethical way to determine whether investigational drugs and vaccines help or harm. Each disease scenario calls for its own informed assessment of appropriate clinical trial designs. Importantly, she says, incorporating adaptive elements or interim assessments might aid in the timely generation of interpretable safety and efficacy data. Properly designed clinical trials also serve as a mechanism to provide patients access to investigational products. PNAS caught up with Borio at a recent colloquium on randomized controlled trials at the New York Academy of Sciences.

PNAS: You led the agency’s efforts in responding to the Ebola epidemic in three different countries in West Africa. Among the logistical challenges to conducting clinical trials of investigational products in resource-poor, epidemic settings, which were the most daunting?

Borio: The FDA was just one component of the overall response to the 2014 Ebola epidemic. I led the agency’s response to this epidemic in my capacity as Assistant Commissioner for Counterterrorism Policy. First of all, the rewarding part of the experience was that everyone quickly came together around the common goal of doing everything we could to save lives. Early on, the agency recognized the tremendous challenge before us: the US government was involved in the development of most of the investigational products, but the human toll was happening overseas in a region where the US government’s clinical research efforts had virtually no footprint. So we built bridges with regulators in the three affected countries in West Africa and continued working closely with the World Health Organization. We needed to have an open dialogue with West African regulators to understand the context in which these investigational products might be administered and how they could be assessed to evaluate whether they were benefiting patients or not. Because public health control measures were helping, thankfully, to bring the epidemic under control, we knew we would have a narrow window within which to conduct trials to learn whether the most promising investigational products were safe and effective. So while there was tremendous hope that the investigational products could be used to help stem the epidemic, there was considerable uncertainty as to whether the products would help patients, do nothing, or cause unintentional harm. We knew it was essential that clinical trials be designed to provide interpretable data—-with respect to both safety and efficacy—not only to protect patients in the ongoing epidemic, but so that the global community could learn whether investigational products are safe and effective for broader use in the future. The US mounted several clinical trials for vaccines as well a therapeutic product.

PNAS: At the colloquium, we heard a number of speakers emphasize the need for alternative trial designs to complement or replace RCTs in some scenarios. What are some examples in which alternative
Broadly speaking, in principle, trials should be adequate and well-controlled, regardless of their specific design. And I should clarify that the reason that is so important is because, at the end of the day, trials need to provide interpretable data that can inform healthcare providers, patients, and regulators. The design of the three vaccine trials conducted in West Africa could all be considered “adequate and well-controlled.” The trials in Liberia and Sierra Leone provided important data regarding safety and immunogenicity of the products as well as impacts on different age groups, even though the epidemic was waning by the time the trials got under way. The ring vaccination design used for the trial in Guinea was a cluster-randomized trial. It targeted patients at high risk of exposure to the Ebola virus. The published results look very promising, and this design has now become the standard response to any new outbreak of Ebola-Zaire virus. Finally, the ZMapp trial launched in the US and Liberia was an RCT of ZMapp versus standard-of-care that included Bayesian and adaptive elements that would enable an investigational drug that was shown to have efficacy against Ebola to be incorporated into the evolving standard of care, in hopes that an effective therapy would be identified as soon as possible (1).

PNAS: What are your views on the utility of platform trials—in which different sponsors working in concert test multiple interventions simultaneously—for obtaining high-quality standardized data on investigational drugs and vaccines? What are the challenges facing platform trials?

Borio: Platform trials can provide a valuable tool; it does not make sense for each sponsor to mount separate trials from scratch every time they want to develop a new product for a given disease or epidemic. The ZMapp study for Ebola was originally envisioned as a platform trial. To that end, investigators from Nebraska, Emory, and the National Institutes of Health ranked the investigational therapeutics to determine what would be tested initially. The idea was to compare the other therapeutics with the winner or test combinations of therapeutics. But, happily, the epidemic waned, and there weren’t enough patients to carry out additional tests. I truly believe that platform trials are the way to go during public health emergencies. As my colleagues, Edward Cox and Nicole Lurie, and I described in an article in the New England Journal of Medicine in 2015, streamlined development programs with a common protocol that do not necessarily have the traditional phase 1, 2, and 3 structure might serve us well in some emergency situations (2). It would help to quickly determine what works and what does not, and provide rapid access to patients who desperately want the chance to receive investigational products. PNAS: The Innovative Medicines Initiative, a 3.3 billion-euro public–private partnership between the European Union and pharmaceutical industry, is aimed at improving the overall drug development process by exploring ways to shorten the time to reach clinical proof-of-concept, to increase the success rate of medicines prioritized by the World Health Organization, and to develop treatments with little market incentive. What are the challenges to launching similar initiatives in the United States?

Borio: I think the key challenge is one of collaboration in a competitive space. We saw companies come together to respond to the Ebola epidemic, but once the epidemic waned, the sense of urgency was lessened, and there was less motivation for collaboration. Also, there is no single entity in the United States today that is in charge of conceptualizing, developing, and implementing such platform trials, particularly during public health emergencies. There is clearly a great need toward such models here in the US.

PNAS: Although the need to accelerate therapeutic development is undeniable, the drawbacks of approving products on the basis of limited efficacy data hardly need overstatement. What are your views on such provisional approvals?

Borio: Once they are on the market, it’s really difficult to remove ineffective products that patients perceive as helping them. And it’s always possible that it really is helping some small group of patients with particular disease characteristics. This is one example of where regulatory science becomes extremely important, in diligently ensuring that we are making scientifically sound decisions. The strength of the FDA is that it is a science-based regulatory agency; it’s not the law but the science that drives its actions, and the legal framework under which [the] FDA operates is the most flexible in the world. We can exercise flexibility when the flexibility is supported by sound science.

PNAS: With the fragmentation of patient populations driven by advances in precision medicine, will it become increasingly difficult to conduct RCTs for certain conditions in the future? Take oncology, for example. With targeted drugs tailored for ever-smaller subsets of patients with particular genetic defects, conducting RCTs may pose a challenge.

Borio: The question really is: What types of trial designs are most suited for a given disease or condition? There is a lot under the tent of “adequate and well-controlled.” Ultimately, what we need are properly designed trials that provide interpretable data to inform decisions made by healthcare providers, patients, and regulators. It’s important not to generalize what’s optimal for one therapeutic area to others. In oncology, the approach of targeting drugs to small patient subgroups is entirely...
appropriate, given the predictable nature of most oncologic conditions and the state of science associated with the pipeline of investigational oncologic products, but that may not be the case for other areas. In the end, there is no one-size-fits-all approach.