Congress and FDA nominee heap love on ‘adaptive trials’

By Kelly Servick | Apr. 7, 2017, 5:45 PM

In 2006, Scott Gottlieb, then a deputy commissioner at the U.S. Food and Drug Administration (FDA), stood before an audience of clinicians and researchers to sing the praises of a new approach to drug trials. Instead of locking in a study’s design from the start, researchers could build in options that would allow them to adjust along the way, based on the data they had collected. They could make the trial larger or smaller, for instance, add or remove arms, or change how incoming patients get assigned to them. Gottlieb predicted such adaptive trial designs, the topic of the conference he attended that distant summer in Washington, D.C., would “tell us more about safety and benefits of drugs, in potentially shorter time frames.”
This week, as President Donald Trump’s nominee to head FDA, Gottlieb sat before Republican lawmakers hungry for promises of “shorter time frames” for drug and device approvals, and again expressed his zeal—repeatedly—for adaptive trial designs. If confirmed to be FDA’s head, as expected, Gottlieb suggested he’d promote wider use of the approach.

But for all their promise, many adaptive trial features still aren’t commonplace. And Gottlieb will face a number of obstacles to encouraging their wider use, experts tell Science Insider.

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Gottlieb’s 5 April confirmation hearing before the Senate’s health committee was relatively smooth. And at times, the physician and health policy veteran offered adaptive trials as a possible solution to a number of problems raised by senators. When Senator Mike Enzi (R–WY) remarked that companies often have to “fight it out with FDA” in a lengthy process to get a drug approved, Gottlieb said new tools like flexible trial designs could make the agency’s review more efficient. He cited adaptive trials in explaining to Senator Tim Scott (R–SC) how the agency could incentivize new treatments for pediatric cancer. And when Senator Richard Burr (R–NC) wondered whether investigators should bother with double-blind studies at all, Gottlieb deflected with an assurance that FDA could at least accept adaptive trials, with their looser rules for randomizing patients.

“Adaptive clinical trials’ is one of those buzzwords that get brought up all the time,” says Rachel Sachs, an innovation and health law professor at Washington University in St. Louis in Missouri, and “there is definitely real momentum to actually do more trials this way.” She notes that in the 21st Century Cures Act, signed into law this past December, Congress required that FDA issue guidance and hold a public meeting to clarify how drug sponsors can use adaptive trials in their submissions for drug and device approvals. Legislation that must pass this year to reauthorize FDA’s user fee program commits the agency to create a pilot program to review such innovative trial proposals and the computer simulations that often guide them.

Lot of love

Why all this love for adaptive trials? "You have the ability to learn so much more about response to a drug or a device by being more flexible," says William Barsan, an emergency physician at the University of Michigan in Ann Arbor who runs such trials for neurological conditions.

In traditional randomized controlled trials, researchers typically aren’t allowed to change the rules as they go along—they stick to processes that randomize patient assignments to a treatment or placebo group, and wait until the end of a predefined study period to learn how they fared. Adaptive designs, in contrast, allow researchers to review results before the study’s predetermined endpoint. They might then assign more participants to treatment groups in the study that are performing better, thus more quickly providing patients with the most promising treatments or doses, and without staging a large and costly trial for each
Some adaptive elements are already common in clinical trials. Many trials build in the option to pull the plug on the whole trial if early evidence shows a drug is highly effective—or totally useless. And some drugs have already been approved based on more complex adaptive designs. A phase II trial of the diabetes treatment dulaglutide, approved in 2014, determined which of several doses should be advanced to the next phase of the trial based on predictions of patients’ improvement—even before they reached the study’s 1-year endpoint.

But that study design “didn’t make as much of an impact on the world as I thought it would,” says Donald Berry, a biostatistician at the University of Texas MD Anderson Cancer Center in Houston and a collaborator on the trial. And in general, complex adaptive trial features continue to be the exception, not the rule. There are few hard data on how many such trials are proposed to FDA, but a recent study of applications for premarket approval to the agency’s Center for Devices and Radiological health found that of 225 submissions between 2007 and 2013, only about 10% contained adaptive designs.

Complicated and intimidating

Some biostatisticians may be hesitant to deviate from designs they already know FDA will support, says Berry, and may be intimidated by the complexity of adaptive trials. “You don’t learn this in universities or in your graduate program,” he says. “One has to almost serve an apprenticeship as a statistician.”

A recent survey of researchers’ attitudes toward adaptive trials—part of a National Institutes of Health and FDA-funded project on which Berry and Barsan collaborated—also found that biostatisticians were also generally less optimistic than other stakeholders about the validity of conclusions from adaptive trials. Some fear that dropping arms or changing randomization rules based on data in the trial will introduce problematic bias to the results, Berry says, though study conclusions can be adjusted to take potential bias into account.

FDA, for its part, has shown plenty of enthusiasm. Its leadership, including outgoing the commissioner, cardiologist Robert Califf, has long promoted adaptive trials, and the agency put out draft guidance on the subject in 2010. Now, Gottlieb is taking up the torch, and plugged some cutting-edge concepts at this week’s hearing. When Senator Robert Casey (D–PA) suggested that he has been dismissive of the importance of phase III studies—the last and often most expensive preapproval trial phase—despite evidence that they can reveal crucial drug shortcomings and safety issues, Gottlieb offered a work-around. “I’m not so sure insofar as I’m critical of phase III trials,” he replied, but “with more modern clinical trial designs, you could compress the phase II and phase III clinical trials into one big, adaptive design.”

That sounds a lot like GBM AGILE, an international phase II study of brain cancer treatments launched in 2015, on which Berry is a co–principal investigator. In this design, a drug that performs well in the multi-armed comparison study will seamlessly move to a “phase III” portion of the trial. Incoming patients will also be assigned preferentially to the drugs that have so far performed the best in people with their cancer’s genetic subtype.
The model “certainly hasn’t taken the world by storm,” says Berry, but he sees the adaptive trials field buoyed by the enthusiasm of FDA and Congress—bodies caught between anxiety over the high cost of traditional clinical trials and a push for faster drug access that, at its extreme, might jeopardize patient safety. “In a way, it’s a compromise,” he says, “between the old school, which is driving us into bankruptcy, and the school that [would] allow any patient who wants any experimental drug to get it.”

Gottlieb, too, seems to be hoping an emphasis on adaptive trials will help him steer that middle course. At the hearing, he proclaimed the choice between quick drug approval and high safety standards “a false dichotomy.” When Senator Scott asked him to elaborate on that false dichotomy, he cited sections of 21st Century Cures that promote computer simulations and adaptive trials: “This is one place, if we’re doing our jobs right, we can have our cake and eat it too.”
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