Industry, FDA Warm to "Adaptive" Trials

Bridget M. Kuehn

HOPING TO MAKE CLINICAL TRIALS more efficient, pharmaceutical companies have begun embracing more flexible trials that evolve based on the data they generate. In recognition of this trend, the US Food and Drug Administration (FDA) has begun drawing up a series of guidance documents for such trials. But these so-called adaptive trials also have drawn criticism that their results are more difficult to interpret and more vulnerable to unblinding and bias.

The principle difference between adaptive clinical trial designs and traditional designs is that the data in adaptive trials are analyzed on an interim basis and used to dictate the future course of the trial, said Donald Berry, PhD, chair of the department of biostatistics and applied mathematics at the M. D. Anderson Cancer Center in Houston.

For example, in a traditional dose-finding trial, patients may be randomized in equal proportions to 4 different doses of a drug or a placebo and those groups remain constant throughout the trial. In an adaptive design, early responses to the doses might be used to alter the number of patients randomized to each group, with patients entering the trial being disproportionately added to dosage groups experiencing the greatest response. An advantage to this arrangement is that it may allow the researchers to more quickly determine whether these doses produce a statistically significant response, to drop a dosage arm altogether, or to end a trial more quickly if there is no response. These trials also require fewer patients to achieve statistical significance and allow more patients to receive better treatment during the trial, according to Berry.

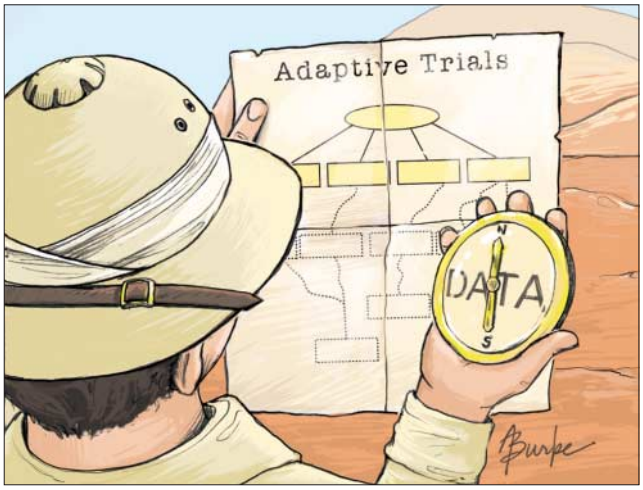
To carry out such designs in blinded trials, investigators must do a tremendous amount of planning in advance using computer simulations and other research tools to predict early outcomes and predetermine modifications, said Berry. Once the trial begins, the data monitoring committee is charged with analyzing the interim data and selecting the appropriate predetermined modifications.

In the spring of 2005, the Pharmaceutical Research and Manufacturers of America assembled a working group of 6 representatives from various pharmaceutical companies to evaluate adaptive trial designs, facilitate their use, and help gain regulatory acceptance for such trials. The group produced a white paper on the topic; the executive summary of the document was published in May (Gallo P et al. *J Biopharm Stat*. 2006;16:275-283), and the complete white paper is slated for publication later this year. "We endorse routine consideration of adaptive designs for clinical trials and encourage critical evaluation of when and where they can be appropriately deployed," the authors note in the summary.

FDA officials have also recently expressed optimism about the potential of such trials. In a speech at the Conference on Adaptive Trial Design in Washington, DC, Scott Gottlieb, MD, deputy commissioner for medical and scientific affairs at the FDA, discussed how adaptive trial designs might fit into the agency's more than 2-year-old Critical Path initiative (http://www.fda.gov/oc/speeches/2006/trialdesign0710.html). "If new scientific tools and approaches could help us learn more about the safety and efficacy of new medicines perhaps more quickly and earlier in the development process, FDA wants to make sure that our own regulatory requirements are recognizing these tools and providing the appropriate flexibility so sponsors can make use of them," Gottlieb said in a written statement.

Others at the agency offer a more tempered message. In a commentary published on July 17 in an online edition of *Statistics in Medicine*, Robert Temple, MD, director of the FDA's Office of Drug Evaluation 1, provides an overview of the agency's experience with such trials (Temple R. *Stat Med*. July 17, 2006. doi: 10.1002/sim.2631). "The agency is listening to all proposals," Temple said. "We do not really have fixed ideas, except that we definitely do not want to be fooled by outcomes that are not real," he said in the commentary.

As both critics and proponents of adaptive designs point out, the designs have flaws and may not be appropriate in all circumstances. And debate continues about whether the flaws can be resolved and how, under what circumstances the trials are appropriate, and whether these trials are an improvement over traditional trials.



Pharmaceutical companies and the Food and Drug Administration are considering the use of adaptive clinical trials—studies that are modified while they are in progress, guided by emerging data—as a way to speed new drugs to market.

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FLEXIBILITY, LIMITATIONS

Adaptive designs are not new and have been used in various forms, such as sequential trials that are stopped early based on safety data. However, recently there has been an upsurge in interest in modifying a trial based on emerging results, explained David DeMets, chair of the department of biostatistics and medical informatics at the University of Wisconsin in Madison. While there is little argument about the value of adaptive designs for early clinical trials, there is controversy about using them in later trials.

According to Gottlieb, an advantage of adaptive trial designs that are changed based on emerging data is the potential to better target patient subsets using new technology. He explained that while traditional trials focus on a cross section of the general population, adaptive trials would be able to make use of proteomic or genomic markers to predict patient responses and quickly identify subsets of patients who appear likely to respond to treatment. "These biomarkers could allow the study to be 'enriched' with such patients or allow the primary end point to become the effect in those patients," he said.

But along with these potential benefits come greater complexity. "The logistics of running the trial are more complicated," Berry said.

Gallo and colleagues note that adaptive designs require rapid—preferably electronic—data collection and may work best when study end points or other measurable outcomes occur relatively early in the trial. An integrated system is also needed for collecting data, managing drugs, and communicating with participants in such trials, and sophisticated software programs are required that are capable of handling the more complex statistics involved in these studies.

Michael Krams, MD, assistant vice president of adaptive trials and clinical development at Wyeth Pharmaceuticals and chair of the working group, said an adaptive trial approach looks most promising for dose-finding trials or for seamless phase 2/phase3 trials, which may allow investigators to treat the data collected in both phases as a single data set.

But Thomas R. Fleming, PhD, chair of the department of biostatistics at the University of Washington School of Public Health and Community Medicine, who outlined some of the problems associated with adaptive designs in a commentary published in advance online in the journal *Statistics in Medicine* (Fleming TR. July 18, 2006. doi: 10.1002/sim.2641) sees a more limited role for these trials. "In early-stage trials, added flexibility would be appropriate to allow the data to guide where you are headed," he said. But such flexibility could be problematic in phase 3 trials, he explained, because adaptive trials have less statistical efficiency and their results are more difficult to interpret. In addition, because interim results are often misleading, basing trial design changes on such results is risky, he said.

Adaptive designs also seem to overemphasize statistical significance over clinical significance, added Fleming. "The primary goal [of a definitive randomized clinical trial] should be to obtain a statistically reliable evaluation regarding whether the experimental intervention is safe and provides a clinically meaningful benefit," he said in his commentary.

The biggest concern voiced by many critics is that adaptive trials may be more vulnerable to unblinding and bias if interim changes in trial design inadvertently reveal early results to sponsors, investigators, or patients, Fleming said.

Susan Ellenberg, PhD, associate dean of the University of Pennsylvania School of Medicine, in Philadelphia, explained that history has demonstrated the importance of keeping interim data secret because "when people know what the interim data are it effects the trial." She explained that the release of interim data could cause investigators to treat patients differently or change the type of patients that are added to the trial. Such interim data could also influence financial markets.

"A lot of people, even advocates of adaptive designs, are thinking about this and seeing how we could manage this and the flexibilities of adaptation without risking the integrity of the trial," Ellenberg said.

But Berry argues that some information can also leak from trials with traditional designs. "It's a possible stumbling block, but I don't think it should or will be overly limiting."

Krams and colleagues acknowledge this concern in their white paper summary and said that adaptive designs should seek to limit the amount of information that can be inferred by observers. But the need for careful planning, steps to prevent operational bias, and statistical adjustments are all issues that can be easily addressed, said Krams.

OTHER CONCERNS

Proponents and critics of adaptive trials are also debating the data monitoring committee's role in such studies. These designs give the data monitoring committee a much larger role than they play in traditional trials. In adaptive trials, the committee would still be responsible for ensuring patient safety but would also be required to analyze interim data on a drug's performance in the trial, reevaluate the design of the trial, and potentially make business decisions, Krams said. "It's a vastly expanded [charge]. There is lots of discussion about how to do this and there's no consensus about how this best can be done."

Fleming said he fears these added responsibilities may overburden them. Pharmaceutical companies are also wary about these independent committees making complex and potentially costly business decisions.

Others worry that having access to the interim results might bias the data monitoring committee's decisions on which changes to implement. "It's not clear how the data monitoring committee would implement modifications without being biased," said DeMets.

Additionally, DeMets said data monitoring committees are reluctant to make

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design changes based on early trends because they know such results can be unreliable. "I'd be reluctant to make anything adaptable based on early results," cautioned DeMets. Berry argues that careful pretrial planning by the principal investigator could alleviate this concern. He said that ultimately, the data monitoring committee will be making "decisions previously spelled out by the company." Others have proposed including a pharmaceutical company representative on the committee. Krams suggests that this could be done without compromising the integrity of the trial by selecting a representative who is not immediately involved in the trial and by putting a "firewall" between that representative and employees involved in the trial.

But Fleming said it would be unethical to give a representative of the pharmaceutical company access to interim trial data while withholding that same data from the patients. "If the sponsor views these results to be sufficiently informative to be useful to guide design changes, then why don't patients have a right to have the same access at that time?" he notes in his commentary.

Moreover, some scientists question whether adaptive designs that incorporate modifications based on emerging data are even necessary. DeMets notes that designing a trial based on better assumptions would be more statistically efficient than running an adaptive trial. "Some of us think we ought to be spending more energy doing better intermediate studies, so that the need for adaptive designs would be less," he said. □

National Academies: Barriers and Widespread Bias Harm Women in Science, Engineering

Tracy Hampton, PhD

THE BARRIERS TO HIRING AND PROmotion that women face in the fields of science and engineering are depriving the United States of an important source of talent, according to a new report from the National Academies (http://www.nap.edu/catalog/11741.html).

Four decades ago, women made up 3% of the US scientific and technical work force, but by 2003 they accounted for nearly one fifth. In addition, women have earned more than half of the bachelor's degrees in science and engineering since 2000. However, among individuals earning PhDs in these subjects, 4 times as many men as women hold full-time faculty positions, and minority women with doctorates are less likely than white women or men of any racial or ethnic group to be in tenured positions.

In offering recommendations to promote advancement of women in science and engineering, the report presents the consensus views and judgment of members of the Committee on Maximizing the Potential of Women in Academic Science and Engineering. The 18-member committee, an appointed group including university presidents and chancellors, provosts and professors, former top government officials, policy analysts, and scientists and engineers, included Donna E. Shalala, PhD, president of the University of Miami, who served as chair; Catherine D. DeAngelis, MD, MPH, editor in chief of *JAMA*; Shirley Malcom, PhD, of the American Association for the Advancement of Science; and Alice M. Rivlin, of the Brookings Institution.

The committee revealed a number of findings. For example, with each step up the academic ladder, the representation of women in science and engineering drops substantially. Women are also likely to face discrimination in every field of science and engineering, and evaluation criteria contain arbitrary and subjective components that put women at a disadvantage. Academic organizational structures also contribute to the underuse of women in academic science and engineering.

The report offers a number of recommendations that could improve the working environment for women and allow them to reach their full potential. Trustees, university presidents, and provosts should provide clear leadership in changing the culture and structure of their institutions to recruit, retain, and promote more women into faculty and leadership positions. The report also said that professional societies and higher education organizations should promote equal treatment of women and men, federal funding agencies and foundations should ensure that their practices support the full participation of women, government agencies should set guidelines and enforce existing laws to increase the science and engineering talent developed in the United States, and Congress should encourage adequate enforcement of antidiscrimination laws.

The report states that the barriers to women are a call to action. "Faculty, university leaders, professional and scientific societies, federal agencies and the federal government must unite to ensure that all our nation's people are welcomed and encouraged to excel in science and engineering in our research universities. Our nation's future depends on it," the committee wrote. □

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