Controversy Trails Adaptive Clinical Trials

By Merrill Goozner

Two years after advocates for “adaptive clinical trial design” heralded the first Food and Drug Administration draft guidance outlining conditions for its use, controversy still rages over its applicability, especially in Phase III confirmatory settings.

Stopping trials midstream, changing the size of the patient population or shifting how patients are assigned to the various arms in a trial are the hallmarks of adaptive design. The controversial methods have roiled biostatistics circles for more than 15 years.

Championed as faster, less costly and a better way to identify subpopulations that respond well to particular treatments, adaptive trial design proponents cheered the positive results from a complex Phase II lung cancer trial using adaptive design that involved four drugs and 11 biomarkers. When the results of BATTLE (Biomarkers-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination; see JNCI 102;16:1217–18) were announced in 2010, the sponsors at M.D. Anderson Cancer Center suggested the start of a new era was at hand. Adaptive design would be the gateway to personalized medicine.

But there hasn’t been a surge of Phase III trials using adaptive designs in the wake of the guidance, which has yet to be finalized by the FDA. And at a debate at the annual meeting of the American Society of Clinical Oncologists in Chicago in June, skeptics once again seemed to have the upper hand.

“If the effect is small, as it is in most cancer trials, the adaptive design can lead to enrolling even more patients than group sequential designs,” said Marc E. Buyse, Sc.D., chairman of the Belgium-based International Drug Development Institute. “And what guarantee is there that the patients entering the trial will be the same as the patients who entered before (adaptation)? This is a big regulatory concern.”

Potential Beneficiaries

Proponents continue to hope that adaptive trial designs will be able to identify subpopulations that benefit from particular drugs or regimens, although they admit most cancer trials using adaptive design are likely to wind up being larger than originally planned, not smaller. “It makes sense to adjust the trial based on the interior data you observe,” said J. Jack Lee, Ph.D., a biostatistician at the M.D. Anderson Cancer Center at the University of Texas. “The key is using a short-term endpoint to inform a long-term endpoint.”

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That wasn’t the expectation a half decade ago. The FDA’s Critical Path Initiative, which looked to improved regulatory science to cure the drug industry’s innovation drought, highlighted adaptive trials as one potential pathway to faster drug approvals.

“These new approaches to clinical trials can result in trial designs that tell us more about safety and benefits of drugs, in potentially shorter time frames, exposing fewer people to experimental treatments, and resulting in clinical trials that may not only be more efficient but are more attractive to patients and their physicians to enroll in,” said Scott Gottlieb, M.D., then deputy commissioner for medical and scientific affairs at the FDA and now a fellow at the conservative American Enterprise Institute. He was speaking at a 2006 conference on adaptive trial design in Washington.

And there was reason to hope adaptive trials would lead to shorter, less costly trials with fewer patients, especially in oncology. The FDA has approved numerous drugs over the years based on one variation of adaptive design: stopping a trial early. Sometimes it was because the results were so clearly positive that it would be unethical to deny treatment to patients in the placebo arm of the trial. Sometimes companies called a halt to trials when preliminary data indicated the treatment would prove useless or was causing harm.

Either way, stopping a trial early fit the broader definition of adaptive design — as long as the trial sponsors had indicated in advance when they would evaluate the data to make the protocol shift. “Plan big and stop early if the results are obvious at a preplanned earlier look at the data,” is how one FDA official explained the format.

Concern Over Study Bias

But regulators remain concerned about the potential biases that can lead to Type I or false positive errors when trial sponsors shift protocols based on an interim analysis, even if the point at which the interim analysis took place was pre-specified. For instance, in a complex trial with four arms using three different drugs and a placebo, an interim analysis might show that one or two of the experimental drug arms were not generating many positive results. The trial organizers could decide at that point...
to assign newly randomized patients either to placebo or the arm generating the most positive results, thus maximizing the chance for an overall positive outcome. “Bias can be introduced by knowing the results associated with various choices of endpoints, subject subsets, or analyses, and choosing the most favorable,” the guidance warned.

In addition, if patients know the pre-specified point when the interim analysis would take place, they might delay enrolling in the trial until their chances of getting the more successful treatment increased. And “should he patients receiving the other treatment feel?” asked Buyce. “Should they drop out of the trial?”

Such concerns have limited the method’s deployment in confirmatory trials. According to Lee, a 2008 survey had identified just 50 clinical trials that used some form of adaptive clinical trial design. A more recent analysis, he said, came up with 72 trials with planned interim analyses. Fifty-six were stopped early with futility being the reason 70 percent of the time. The FDA could not name a single drug whose approval was based on a trial where patient assignment was changed mid-stream. “Success depends on finding good biomarkers to guide patients to assignment to better treatments,” Lee said. “Unfortunately we don’t have good markers or good treatments.”

Researchers who work closely with industry on new drugs seeking regulatory approval recognize the pitfalls of tampering with the original protocol in a confirmatory trial. “Going down in number is generally not advised,” said William Sietsema, Ph.D., vice president for global regulatory strategy at Cincinnati-based INC Research, Inc., a contract research organization that conducts numerous clinical trials for industrial clients. “You could end up with a trial without enough patients. Most companies would not shrink a trial size as the result of an interim analysis. They might make it bigger, or they might stop it, but they wouldn’t shrink it,” he said.

He also cautioned against “play the winner” designs that increase the number of patients being randomized to arms that show the best results in an interim analysis. “That is most often used in early phase trials, like a Phase I or early Phase II trial where you’re really trying to identify the best dose level; such trials tolerate bias pretty well,” Sietsema said. “But you wouldn’t use a play-the-winner model in a Phase III trial because the potential for bias could lead to a wrong decision and the FDA would object.”

Yet adaptive designs remain rare for early stage trials, too, even though regulators might have fewer objections and investigators could gain valuable experience in managing the process. “It’s paradoxical that adaptive design is not being used more in Phase I trials where it’s very useful,” Buyce told the ASCO forum, “and it’s not very much used in Phase III trials, which is where all the excitement is.”

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**Urology Meeting Highlights Prostate, Bladder Cancers**

*By Mike Fillon*

The United States Preventive Services Task Force (USPSTF) did not back off its controversial recommendations against PSA-based screening for all men, regardless of age, at the American Urological Association (AUA) Annual Meeting in Atlanta in late May. If anything, it dug its heels in.

Reaction came fast and loud from urology organizations, patient advocacy groups and AUA meeting attendees, starting with AUA president Sushil I. Lacy, M.D. “The AUA is outraged at the USPSTF’s failure to amend its recommendations on prostate cancer testing.

In October 2011, the USPSTF said its research found that routine PSA-based screening resulted in little or no reduction in prostate cancer-specific mortality and could cause unnecessary harms from evaluation and treatments. The Task Force is made up of 16 experts in prevention and evidence based medicine including cancer researchers. There weren’t any urologists on the Task Force. Their recommendation was based solely on a systematic review of available published evidence including clinical trials and a review of public comments.

Despite the objections at AUA, the USPSTF did not change its position. “Many people who commented on the