

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Adaptive Trial Design

Donald A. Berry, PhD
Chairman
Department of Biostatistics and
Applied Mathematics
The University of Texas M. D. Anderson
Cancer Center
Houston, Tex.

H&O What deficiencies of traditional clinical trial design is adaptive trial design intended to address?

DB Traditional clinical trial design—called frequentist design—is based on statistical inferences and has been the bedrock of science within the realm of oncology and in medicine more generally for decades. A great virtue of frequentist design is its rigor and narrow focus on the specific experiment, but these qualities can be limiting, from scientific, financial, and ethical perspectives, precisely because of their inflexibility. For example, in a dose-response trial, a statistical calculation is made regarding the comparison between the agent under investigation and placebo or active control therapy. The treatment arms are assigned an equal number of patients and the trial is run. When the investigators see the data, it is quite possible—and even likely—that they wish they had designed the trial differently. Adaptive design allows for reviewing the data accruing in a trial while it is ongoing, with the notion of modifying the trial's design to, for example, focus on doses that seem to be most interesting, therapies that are doing better, dropping treatment arms, stopping early, expanding accrual, or having a seamless transition from one developmental phase to another. A common form of adaptive trial design uses the Bayesian paradigm, which is one of learning. As information becomes available, researchers can update their knowledge about the unknown aspects of the process that is producing the information. The fundamental tool for learning under uncertainty is Bayes' rule. Unlike the frequentist approach, in the Bayesian approach, uncertainty regarding

the various hypotheses (such as whether a drug is effective) is measured by probability, which can be calculated conditionally upon the available results. The seemingly simple notion of looking at data as it accrues is actually revolutionary in drug development.

H&O What is the history of adaptive trial design?

DB Adaptive design is quite old. Despite the rigidity of frequentist design I described, there have been changes over time in the way trials are conducted. In the context of randomized trials, the first type of adaptive design gained currency over 40 years ago: interim analysis with the goal of stopping the trial early if the results answer the question addressed with sufficiently high precision. The criteria for stopping a trial early, sometimes called the stopping boundary, are almost always conservative, which leads to few trials qualifying for early closure. An important landmark in the history of adaptive design was approximately a decade ago when the Center for Devices and Radiological Health (CDRH) at the US Food and Drug Administration (FDA) encouraged a Bayesian approach to clinical trial design in response to a general call for more efficient trials that preserved scientific rigor. Until that point, medical device development had been driven more by uncontrolled experiments and expert testimony than by randomized clinical trials. Because device manufacturers tend to be small companies, they viewed possible new requirements to run large, randomized clinical trials as onerous and limiting. In response, due to the companies' lobbying efforts, Congress passed legislation requiring the investigation of devices to be "least burdensome." CDRH encouraged companies to take a Bayesian approach as one way to comply with this new mandate while at the same time increasing the scientific rigor of its device clearance process. More recently, Bayesian adaptive trials are being considered by the FDA's Center for Drug Evaluation and Research.

H&O Is it difficult to set up an adaptive design?

DB Usually, yes. In the adaptive designs that I promote, the trial is set up completely prospectively. The investigators and sponsors decide on the trial's goals; some examples are to treat as many patients as effectively as possible, to

expose the fewest patients to what turns out to be ineffective therapy, to have a maximally informative trial within a fixed budget, to choose a dose or therapeutic strategy as effectively and as economically as possible for a subsequent experiment, etc. There may be constraints to the design, such as that no more than 3 patients are to be assigned to a dose until they have been followed long enough to ensure that there are no untoward toxicities. There may be logistical constraints, such as that the data can be updated only once a month. The overall theme determines the design subject to these constraints. However, the necessary mathematical calculations may be quite complicated. For example, each stage of the trial may require finding the probability that the trial will eventually be successful (in whatever sense is relevant) based on the data available so far. And the number of possibilities at each stage can be enormous. Therefore, describing the design in writing can be difficult. Moreover, it is important that the investigators understand and agree with the design; they must be educated about the various scenarios to ensure that the actions taken on the basis of the data are consistent with their overall gestalt regarding appropriate actions.

H&O How does adaptive design make use of computer simulations?

DB Adaptive designs can be and generally are quite complicated. Investigators and regulatory bodies have to understand them, and they must be persuaded that the designs are doing what they claim and that their “operating characteristics” are acceptable. Operating characteristics include false-positive rate (Type I error), statistical power (the probability of correctly concluding that a drug is effective), sample size distribution, trial cost, etc. When a design is complicated, these characteristics cannot be found by solving neat mathematical formulas. Instead, simulation is necessary, which means making assumptions about the various parameters associated with the treatments—such as, when finding a Type I error rate, that the experimental treatment is no better than the control—and generating patient histories according to the trial design. Each such simulation may require millions or billions of calculations, and to find the operating characteristics with sufficient accuracy requires repeating this process many thousands of times. The total number of calculations can be mind-boggling. We use powerful computers that were not available 20 or even 10 years ago. Many adaptive trial designs now in use would not be possible without computer simulation.

H&O How does adaptive design work in phase I trials?

DB In oncology, phase I trials have for many years been adaptive as they attempt to find the maximum-toler-

ated dose (MTD). A traditional but adaptive trial for a cytotoxic chemotherapy is called the 3+3 design. It is not particularly sophisticated. Three patients are assigned to a chosen dose, and if no toxicity is seen at that dose, three patients are assigned to the next higher dose, and so on until toxicity is observed. If at any point, among the three patients, two or three experience a limiting toxicity, the trial stops and the previous dose is considered the MTD. If one patient among the three is observed to experience limiting toxicity, the cohort is expanded to another three patients at the same dose. If none of these additional patients experiences the toxicity then the dose is increased as before and if one or more experiences the toxicity (for a total of at least two), the trial is stopped and the previous dose is considered the MTD. This type of design is adaptive in the sense that the available data affects the future course of the trial. But this design has a number of flaws, including the inability to decrease the dose and to otherwise explore the dose-toxicity relationship. Furthermore, the adaptations are based only on the data at the last dose used rather than on the entirety of the information in the trial. Such a design does not find the MTD with much accuracy. More recently, in the last 10 years, a Bayesian approach called the continuous reassessment method (CRM) has been introduced. The CRM allows for increasing and decreasing doses being assigned and for deciding when the MTD is sufficiently confirmed.

H&O What is the role of adaptive designs in the transition from phase I to phase II?

DB An important aspect of adaptation is seamlessly switching from one phase to another. Phase I/II designs are becoming popular. In some designs, once the MTD is determined, the emphasis shifts to a measure of efficacy (eg, tumor response). All the patients are used in assessing both efficacy and toxicity. One might even introduce randomization to some control therapy at an intermediate point of the trial.

H&O How does adaptive design differ when it is used for biologic agents instead of cytotoxic agents?

DB Biologic agents have completely changed the landscape of clinical development in oncology. On the toxicity side, there may not be an MTD. On the efficacy side, biologic agents may not cause a tumor to shrink and yet still have an important clinical effect. Moreover, some effective biologic agents have little or no benefit except when used in combination with other agents. All of these issues add to the difficulty of any development program—and they all invite adaptation. As I have indicated previously, information is the stuff of adaptation. Early information is available for biologic agents, namely, the biological effect. Any relationship with clinical effect can

be modeled, and the parameters of the model updated based on data accruing in the trial. An additional aspect of biologic agents is that they may affect—and indeed, may be developed to target—patients with particular subtypes of disease. Here too adaptivity is possible and even critical. One sets up a trial design that enables learning about the types of patients who benefit from the particular therapy or therapeutic strategies under consideration.

H&O What tumor types or settings are most amenable to adaptive trial design?

DB All tumor types and all settings are candidates for adaptive design. However, the ability to adapt may be limited by the availability of response information. For example, the prognoses of adjuvant breast cancer patients are extremely good, and improving all the time. Their disease may never recur and if it does, it may not recur for many years. So a trial may be fully accrued before much information becomes available. On the other hand, there will be some available information and it never hurts to plan ahead for using such information, should it be helpful.

H&O Are there problems inherent to analyzing data before they are finalized?

DB The short answer is yes, but this is not a limiting toxicity, so to speak. Adaptive trials are designed with full knowledge that immature data can be misleading. False-positive observations are everywhere. This potential problem is accommodated in the design. Suppose, for example, patients in the early stages of a trial who overexpress a particular biomarker respond quite well to a therapy. When there are many biomarkers, such an observation is expected, but most of the time it is attributable to chance alone. One must build some sort of confirmation into the design. If a goal of the design is to identify subsets of patients who benefit, then simulations are done assuming that there is no treatment effect in any subset. Therefore, if an effect is seen then it is a false-positive. If simulations find a high rate of false-positives, then the design is changed, for example, to ensure that the overall false-positive rate remains below 5%. Statisticians recognize that immature data can present a huge false-positive problem, but we accommodate the issue by adjusting the various design parameters. We recognize the problem from the outset and prepare for it.

H&O Could you discuss medical ethics in relation to adaptive trial design?

DB As indicated, an adaptive trial design should be built with an over-arching theme. One theme that dominates

trial design at my home institution is to maximize the effectiveness of the treatments delivered to patients in the trial. If a treatment combination is doing better than another, it is accorded higher probability of being assigned to future patients. In clinical research, however, people sometimes have trouble learning the obvious. For example, a trial involving hundreds of cancer patients was announced recently. The experimental therapy had a huge and highly statistically significant negative impact on survival—in effect, the experimental therapy was killing people—but the trial was fully accrued and follow-up fully completed. If the trial did not have interim analyses, it was unethical to conduct it. And if it did have interim analyses, then either the data monitoring committee was asleep at the switch or the stopping criteria were so conservative as to be useless and therefore unethical. Had there been any serious consideration of stopping early for futility, the trial would not have gone on for as long as it did. Clearly, employing an adaptive aspect has ethical ramifications. And sometimes not being adaptive is unethical.

H&O Is there an effort to broaden the application of adaptive trial designs across institutions?

DB Yes. There are many efforts in place. The American Society of Clinical Oncology (ASCO) has a joint initiative with the FDA to this end. Additionally, the FDA has its Critical Path Initiative. They are very serious about supporting innovative trial designs and helping companies incorporate them into drug development. Furthermore, there is a joint consortium of the National Cancer Institute, Centers for Medicare and Medicaid Services, and the FDA called the Oncology Biomarker Qualification Initiative that is dedicated to biomarker development, as well as in innovative designs that utilize biomarkers and imaging modalities. Additionally, many pharmaceutical companies are enthusiastic about adaptive design, sometimes because of its inherent appeal and sometimes because they worry that not being a player in this arena will put them at a competitive disadvantage in relation to other companies. Many companies are getting involved, learning about adaptive design, and running prototype trials.

Suggested Readings

Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5:27-36.

Berry DA. Statistical Innovations in Cancer Research. In: Holland J, Frei T, et al, eds. *Cancer Medicine*. 7th edition. London: BC Decker; 2005:411-425.

Berry D. Bayesian statistics and the efficiency and ethics of clinical trials. *Stat Sci*. 2004;19:175-187.

Berry DA, Eick SG. Adaptive assignment versus balanced randomization in clinical trials: a decision analysis. *Stat Med*. 1995;14:231-246.

Giles FJ, Kantarjian HM, Cortes JE, et al. Adaptive randomized study of idarubicin and cytarabine versus troxacitabine and cytarabine versus troxacitabine and idarubicin in untreated patients 50 years or older with adverse karyotype acute myeloid leukemia. *J Clin Oncol*. 2003;21:1722-1727.