The FDA’s First Moves to Supplant Randomized Controlled Clinical Trials

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The type of protocol design that guides data collection in the FDA’s new drug approval process may seem like an arcane concern to those outside the world of drug testing. The end result is what really matters to patients—whether a new product is considered safe and effective enough to permit access to it. However, the methods that are used to derive the data are crucial to determining the end result. A switch from RCTs to adaptive trials could alter the fates of many potential therapies. Those treatments that are ultimately approved could reach the public sooner and could cost less to test. Perhaps most important, newly approved drugs might reach the market accompanied by more accurate information on their dosing and indications for use.

INTRODUCTION

The touchstone of clinical research is the randomized controlled trial (RCT). This is the design preferred for studies that face academic scrutiny through peer review, and it is the required research paradigm for findings that are submitted to the Food and Drug Administration (FDA) to support New Drug Applications (NDAs). The probative value as well as the greater validity of well-designed RCTs, as compared with most other research methods, is accepted throughout the scientific community.

That situation is about to change. The FDA announced in July that it will be promoting the development and use of an alternative approach—the adaptive trial. Proponents contend that this new design will be faster, more efficient, and more accurate, because it can be adjusted as a study progresses. Adaptive trials are particularly well suited to testing drugs in the dawning era of “personalized” pharmaceuticals, and several drug companies are actively exploring the use of this new technique.1 By seeking to lead the way, the FDA is legitimizing the potential of adaptive trials as a reform that represents more than the concerns of a single constituency.

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THE ORIGINAL CASE FOR RANDOMIZED CONTROLLED TRIALS

The logic behind the RCT research design seems unassailable. Before the efficacy of a new drug is actually tested, it is only theoretical. Even the most promising results from laboratory experiments and animal studies cannot always be replicated in humans.

Reliable testing must ensure that drug effects are observed in a representative sample of patients and that the effects are isolated from possible confounding factors. In RCTs, investigators study a sample of patients with the disease of interest. Subjects are randomly assigned either to a group of patients who will receive the new treatment or to a control group of those who will not. Random assignments protect against selections based on patient characteristics that might influence responses to the treatment.

Because the mere act of receiving a therapy, regardless of its actual efficacy, is capable of producing clinical effects, patients who are not in the treatment group receive a placebo, a medication that is identical in all respects to the study drug except for a lack of the active ingredient. As a further safeguard of objectivity, both patients and investigators are kept ignorant (“blinded”) of patient assignments, making the protocol “double-blind” to prevent the possibility that psychological expectations might influence physiological responses.

At the end of the study period, the two groups of subjects are compared in terms of clinical indicators that reflect the progression of the disease under study. Quantitative differences are analyzed for “statistical significance” to determine whether the findings could have resulted from chance. A significant difference between the groups is taken as an indication that the treatment has had an effect.

RANDOMIZED TRIALS: THE SHORTCOMINGS

What could be wrong with a mechanism that reveals treatment effects with a minimum of confounding bias? The answer is nothing—as long as (1) the study includes a patient sample of sufficient size, (2) it lasts long enough for treatment effects to become manifest, and (3) the treatment is administered in an appropriate dose.

Unfortunately, these conditions can be extremely expensive to ensure, and they can add years to the drug-development process. The demands of the RCT design are major contributors to the high cost and long delays involved in bringing new drugs to the market. A faster, more efficient system would benefit patients and manufacturers alike.

The superiority of the RCT is also less clear-cut for some newer kinds of medications. Although RCTs generate the most valid findings for drugs that are aimed at the general population, these trials are not as well suited for assessing a new breed of personalized medications designed for small subgroups of people. Many new cutting-edge medications that have been developed through genomic research are aimed at patients with specific genetic characteristics or at narrow subcategories of diseases. As a result, the effectiveness of these agents, which can be considerable, eludes all but a small portion of the population.

The key to evaluating these novel therapies is to delineate the patient and disease traits that predict clinical response. For example, some new cancer therapies are effective only for patients with certain...
clinical markers and only for narrow subtypes of the disease.

As a method of testing novel drugs, RCTs can be too blunt an instrument, for several reasons. RCTs include patients without regard to their genetic profile. Unless the study sample is large enough, the trial might include too few patients who would be most genetically predisposed to respond. For those predisposed patients who are included, their results are averaged with those of the others, a practice that can mask underlying effects. Finally, if the RCT has enrolled a pool of patients who are unlikely to respond, the result may be an expensive and time-consuming study that misses the most important clinically relevant findings.

THE PROMISE OF ADAPTIVE TRIALS

The current leadership of the FDA believes that there may be a better way to study drugs, particularly newer products stemming from genomic research. Adaptive trials permit investigators to adjust the protocol as a study unfolds. To accomplish this, researchers discard several pillars of RCTs, for instance, by taking advanced “peeks” at the results, which negates the possibility of full blinding.

Data on outcomes are analyzed according to these peeks to identify patient and disease characteristics that seem most closely associated with responsiveness to a drug. On the basis of these analyses, patients who respond well are reassigned to different dosage groups; this negates the original random assignment of the study’s subjects. These patients are then examined in greater depth to identify factors that can best determine the drug’s probable efficacy.

By identifying the subgroups of patients who are most likely to respond to a new drug early in the testing process, the investigators may be able to complete clinical trials more rapidly and at a lower cost. According to some estimates, this new approach might reduce the number of subjects needed by as much as 30%. This means that drugs can be available to patients sooner, and lower development costs might result in lower prices. Moreover, if the patient and disease characteristics that best predict clinical efficacy prior to FDA approval can be isolated, the new research design may be able to enhance the therapeutic potential of the drugs after they are on the market.

Adaptive trials also have advantages over RCTs in terms of ethical considerations. To fully assess the effects of a drug in RCTs, researchers must ensure that subjects in the control group do not receive it. This means that these patients receive either the existing therapy or none at all. If preliminary results indicate that the new drug is more effective than older forms of treatment, these subjects are denied access to a therapeutic opportunity.

In exceptional cases, a randomized trial may be discontinued if the new drug is discovered to represent a clear clinical advance, but this step takes longer than in an adaptive trial. RCTs also continue to treat a heterogeneous group of subjects, whereas adaptive trials may reveal early on that the new therapy is useless for all but a small subset, thereby sparing other patients the needless risk of adverse side effects.

CHALLENGES TO IMPLEMENTING ADAPTIVE TRIALS

The two keys to successfully implementing adaptive trials are (1) the availability of appropriate information technology and (2) the objective oversight of data analysis.

Midcourse adaptation of trials requires sophisticated analysis of data on an ongoing basis. This means, first, that all records must be computerized and maintained in a form that permits real-time access by investigators. Fortunately for the future of adaptive trials, the use of electronic records in clinical testing is already more advanced than it is in most other aspects of health care. However, further advances in information technology may be needed for computerized data access to realize its full potential.

The oversight of data analysis presents more of a challenge. If investigators intervene in a trial’s design as a study progresses, the opportunity to introduce new forms of bias is tremendous. One suggested solution is to give the task of data analysis to outside experts who have no stake in the outcome of the research. The experts could constitute data safety monitoring boards, which presently oversee data analysis, or they could adopt a different structure.

Whichever approach is used, the FDA will become considerably more involved in ensuring the integrity of pre-market test data.

THE FDA’S FIRST STEPS

On July 10, 2006, Scott Gottlieb, MD, the FDA’s Deputy Commissioner for Medical and Scientific Affairs, described the agency’s commitment to promote the use of adaptive trials. The first step is the development of regulatory guidelines. These guidelines will grow out of the work of an agency initiative known as “Critical Path,” which began in 2004 as an effort to encourage the use of new approaches to the drug-development process.

Among its activities, the Critical Path initiative has formed a collaboration with five drug companies, known as the Predictive Safety Testing Consortium, to share data on the predictive value of laboratory tests for clinical efficacy before the drugs are tested in humans. The FDA and the Pharmaceutical Research and Manufacturers Association (PhRMA) have planned a private conference, scheduled for November 2006, to explore the design of adaptive trials. Results should be available in early 2007.

An important legal and regulatory step in the growth of adaptive trials may be the reauthorization of the Prescription Drug User Fee Act (PDUFA), which is scheduled for consideration by Congress in 2007. This act directs drug manufacturers to pay user fees to the FDA to fund reviews of their NDAs. The FDA may ask Congress to use the reauthorization process as a vehicle for implementing the infrastructure and funding mechanism needed to incorporate adaptive trials into the drug-approval process.

Adaptive trials are not the only focus of the FDA’s interest in improving the methodology of clinical testing. Additional guidance documents are being developed to direct investigators on the use of multiple endpoints in the same trials and on the use of enrichment designs that can increase a trial’s statistical power to detect a treatment effect with fewer subjects. The combination of initiatives could change clinical trial design in many respects.

In May 2006, the FDA addressed related issues in study designs to test new medical devices. The agency issued

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draft guidance on bayesian statistics in medical device clinical trials. The draft recommends the use of bayesian statistical methods of designing and analyzing clinical trial data. This approach applies prior knowledge and accumulated experience to probability calculations, and it would permit the use of pre-existing, legally available information on drug safety and effectiveness to enhance the power of data analyses. Testing could then be completed more quickly and less expensively.

The FDA expects to publish the guidance in final form in the near future. Although this type of revision to product testing addresses an issue apart from adaptive clinical trials, it reflects the FDA’s interest in revising the mechanics of the pre-market approval process on several fronts.

THE FUTURE OF DRUG TESTING

Adaptive trials do not yet qualify as a panacea for shortcomings in the clinical trial process. Important questions remain, such as the capabilities of information systems, the qualifications of interim data analysts, the effectiveness of statistical tools, and the ability of regulators to guard against investigator bias. Even if these logistical problems are resolved, adaptive trials raise another concern: they produce less information than RCTs on the longer-term consequences of new therapies because they speed up the study process. Some drug effects take many months or even years to appear, and a trial that changes its design more frequently may be less capable of detecting the effects. This risk of rapid pre-market trials was highlighted in recent debates over the highly publicized withdrawal of rofecoxib (Vioxx, Merck) from the market. If adaptive trials are not conducted carefully, their use could make a situation worse.

Nevertheless, pharmaceutical science is at the start of a revolution. Genomics and proteomics are creating new kinds of therapies that target patients and diseases with much greater precision. The old ways of testing products no longer offer the best guarantee of effective assessment. The use of a new research paradigm is not an arcane question of concern only to researchers; it may be one of the keys that helps to unlock the full potential of new therapeutic directions.

By taking the first steps to promote adaptive trials and similar methods, the FDA is setting in motion a worthwhile bureaucratic process that could move drug development forward.

REFERENCES