THE NEED FOR SPEED

Adaptive Design May Hasten Clinical Trials

By Charlie Schmidt

It’s no secret that drug development can be time-consuming, costly, and prone to failure. That’s especially true for new cancer drugs, which succeed in clinical trials only about 5% of the time—roughly half the success rate for all new drugs combined, according to a report in the August 2004 issue of Nature Reviews Drug Development. Despite those dismal odds, the cancer drug business is booming: In September 2006, more than 600 oncology drugs were in clinical development; a 10% increase since 2001, according to Kalorama Information, the publishing division of MarketResearch.com.

Those rising numbers have fueled pressure to speed the clinical trials that evaluate new cancer drugs. Both the U.S. Food and Drug Administration and the National Cancer Institute are now investigating adaptive designs that may accomplish that goal. “The way we do things now, it can take 5–10 years to find out if a new cancer drug will work,” laments Mahesh (Max) Parmar, Ph.D., who heads the cancer group at the Medical Research Council trials unit in London. “That’s a long time to wait for results.”

Another reason for the push is to find out whether promising treatments in newer research areas, especially advances in human genomics, will work. “We’re in an era in which we have more promising treatments, so the need to evaluate them quickly is greater,” said Michaele Christian, M.D., an associate director in NCI’s cancer therapy evaluation program. “There’s more opportunity to benefit from clinical research now, and we need to take better advantage of that.”

Experts cite many reasons for the slow pace of clinical trials, among them regulatory burdens, time requirements for subject recruitment and data analysis, and inflexible designs that depend on preset doses and sample sizes. Parmar suggests that too many clinical trials answer just one question at a time, such as how a given drug compares to standard therapy or whether it has any effect on event-free survival. “And it’s hard to say if one question has any priority over another,” he adds. “We need to start answering as many questions about different therapies as we can, in as short a time frame as possible.”

Adaptive Designs

While most scientists agree that clinical trials should be faster, debate still rolls over how to do it. The adaptive designs under discussion now allow drug makers to modify doses and sample sizes according to incoming data. Regulators with the FDA have signaled interest in adaptive designs; the agency is now encouraging companies to investigate trials with flexible enrollment and dosing schemes, in addition to other speed-enhancing features.

Christian co-chairs a new NCI task force that plans to focus on adaptive designs during the coming year. But she cautions that while they could answer a wider variety of questions, adaptive designs won’t necessarily be faster—or even as safe—as the standard approaches used now. “There isn’t any silver bullet here,” she says.

One adaptive design under consideration at the NCI and elsewhere is the continual reassessment method (CRM) for phase I clinical trials. Steve Goodman, Ph.D., an associate professor at Johns Hopkins Bloomberg School of Public Health in Baltimore, describes the CRM as a way to identify the optimal dose according to a prespecified toxicity frequency. First introduced in 1990 by John O’Quigley, Ph.D., a professor of mathematics at the University of California in San Diego, the CRM differs from the more common phase I approach, known as the “three plus three” method.

With this current approach, scientists give a predetermined starting dose to three patients and then proceed to another, predetermined higher dose in three more patients if none among the first group exhibits toxic effects. Should one among that first group have a toxic response, then three additional patients are tested at the starting dose. If none of those additional patients exhibits toxicity, then scientists can give the higher dose to the next group of three. This process goes on until two of six patients at a given dose exhibits toxicity. The prior dose is then used in the phase II study.

By contrast, scientists using the CRM first select a desired frequency of toxicity, which is chosen based on the toxicity’s danger and the possible benefit from higher doses. Statistical methods are then used to modify the dose level up or down, according to how patients respond. Those modifications continue until the dose with the target frequency of toxicity is found. A key difference between the CRM and the three plus three method, Goodman says, is that the CRM uses the information from all patients at each step, making it more efficient. “In the end you
are much surer that you have found a dose with the right risk-benefit balance,” he explains. “It also makes it easier to smoothly transition into a phase 2 study.”

But investigators tend to be nervous about using the CRM because leaps from one dose to the next can be large, Christian says. “Clinicians aren’t comfortable with drugs they know nothing about, so they modify the CRM, causing it to be less efficient,” she says. “The method might call for a fourfold increase in dose, but the clinicians might only feel comfortable doubling it.” These modifications, she suggests, can reduce the time-saving potential of the CRM.

Christian suggests that greater use of accelerated titration designs could also speed up phase I clinical trials. Those designs calls for steadily increasing doses in individual patients until toxicity is encountered, which is a potentially more efficient approach, Christian proposes.

Other adaptive designs focus on later phases in the clinical trial process. Among them are so-called multiarm, multistage studies that simultaneously compare a range of intermediate endpoints (multistage) for many therapies or combinations of therapies (multiarm). Parmar stresses that this approach allows investigators to quickly eliminate drugs that don’t appear to work. “That’s the benefit of the multistage component,” he says. “You can knock out arms that don’t show sufficient promise without having to run every one to its conclusion.”

That approach assumes that the intermediate endpoints correlate reliably with the main objective, which is usually event-free survival. Parmar suggests that the scientists usually know enough about these correlations to make the appropriate call. Therapy-induced changes in prostate-specific antigen levels, for example, could be used to predict survival in a clinical trial of new prostate cancer drugs, he says.

Susan Ellenberg, Ph.D., the associate dean for clinical research at the University of Pennsylvania School of Medicine, acknowledges that flexible approaches to dosing and sample sizes could make clinical trials faster. But she cautions that midstream changes, particularly with respect to sample sizes, could also shine unwanted spotlights on drug development. With most current approaches, she says, sample sizes are set before the study and kept confidential during its course. However, using adaptive designs, investigators can add patients as needed to enhance statistical power, which probably occurs only when a given drug isn’t working as well as hoped, she says.

“What happens when we suddenly tell the world a drug isn’t working as well as we thought it would? That could affect clinicians’ desire to enter the trial, or it could influence the patients they choose to enroll.”

While everyone with a stake in drug development wants new approvals to be faster, even adaptive designs don’t offer clear paths toward that goal. And the ensuing debates will probably become more intense as new directed therapies arising from genomics and other advances in molecular biology emerge.

“I think it’s important for clinical research to be as efficient as we can make it,” Christian says. “But there’s no simple answer to this. Speeding clinical trials isn’t necessarily a straightforward process.”