BY DENISE MYSHKO

ADAPTION

WHILE THE INDUSTRY AWAITS GUIDANCE FROM THE FDA, PHARMACEUTICAL COMPANIES ARE CAUTIOUSLY MOVING FORWARD WITH ADAPTIVE TRIALS.

DR. ROBERT O'NEILL

FOOD AND DRUG ADMINISTRATION

THERE MAY BE OPPORTUNITIES FOR ADAPTIVE TRIAL DESIGNS BUT WE NEED TO BE VERY CAREFUL THAT THE USE OF THESE DESIGNS DOES NOT ADVERSELY IMPACT THE INTEGRITY OF THE CLINICAL TRIAL FOR REGULATORY PURPOSES.

The double-blind, randomized, parallel group design of clinical trials is so entrenched with well-established processes and systems in the industry that to even consider a change in structure may seem like an uphill battle.

But many in the pharmaceutical industry — from pharmaceutical companies, contract research organizations, suppliers and service providers, and regulators — are willing to re-evaluate their drug-development processes to make midcourse trial adjustments. They are discussing the challenges and opportunities and working to build the tools and infrastructure to incorporate more flexible, adaptive trial designs. Adaptive designs appear to hold promise for more efficient drug development by allowing sponsors to adjust the trial as results become known.

"Adaptive trials are one way of helping to push critical decisions earlier in the drug-development process," says Jerald Schindler, Dr. P.H., VP of biostatistics and research decision sciences at Merck Research Laboratories. "With adaptive trials, we may be able to identify earlier that a drug will ultimately fail. And we could identify the potential winners earlier as well."

Adaptive designs can help to dramatically accelerate clinical trials and lessen exposure to risks, says Sylva Collins, Ph.D., VP of global biometrics at Kendle.

"With the cost pressures on the pharma industry, adaptive trials additionally can result in significant cost savings and competitive advantages," she says.

The concept of adaptive designs isn't new, but there has been renewed interest since the Food and Drug Administration released its Critical Path Opportunities List in March 2006. The list describes possibilities for improvement in product development and provides 76 examples of how new scientific discoveries could be applied during

FDA Adaptive Trial Designs Drug Development

DR. MICHAEL KRAMS

medical product development. The Critical Path Initiative is the FDA's effort to modernize the process through which products are developed, evaluated, and manufactured.

The use of adaptive trial designs is one of the agency's suggestions. Bayesian and similar nonfrequentist statistical methods that use prior information and models to develop predictive probabilities could provide a basis for supplementing the traditional methods for human equivalent dose calculations and for maximizing the usefulness of data derived from animal safety and efficacy studies.

Bayesian statistics is a theory and approach to data analysis that provides a method for learning from evidence as it accumulates. The Bayesian approach uses a consistent, mathematically formal method called Bayes' Theorem for combining prior information with current information.

THE **BENEFITS** OF ADAPTIVE DESIGNS

Adaptive design methodologies allow those who are engaged in development to learn more about the safety and potential benefits of new medicines earlier in the development process. These tools also allow drug developers to spend less time and money discovering that a new molecule didn't work or that it had a side effect.

Experts say adaptive designs allow the sponsor to make decisions earlier. This can result in fewer patients being required for drug-development programs. It could also result in shorter drug-development timelines. Another benefit is less time spent on drugs that will never make it to market.

Adaptive trials can be used in all phases of development. But where adaptive trials are most commonly used today are in proof-of-concept/dose response trials. In these studies, it's possible to study more doses than in a conventional trial.

"The benefit is that dose selection for the pivotal trial is easier because we now have better quality information about dose response and the shape of the dose response curve," Dr. Schindler says. "In a pivotal trial, we can start to enroll two or three active doses plus the comparator. Then, over time, the best of the doses can continue and the others drop out. This helps to ensure that the optimum dose is used for registration."

These important studies will be of value as companies start to learn to implement the process of adaptive clinical trial designs, says George Mills, Ph.D., VP of medical imaging consulting for Perceptive Informatics at Parexel International Corp.

"Adaptive clinical design features can be used to speed through sometimes not so productive aspects of early clinical trials, such as dose finding," he says. "The standard process is to select a ladder of doses to find the ideal response level and to look at safety signals. Those early selections and signals, both positive and negative, can reduce the number of patients who may be involved in a clinical trial. As a result, the industry won't need to expose a patient to a lower dose level, which is not going to be productive. Ultimately, we can reduce the number of patients at that level and move to the next one through adaptive clinical trial design."

The keys, experts say, are that the statistical design is properly planned at the beginning, that all of the details are included in the protocol, and that there are enough communications with the FDA around the planning of the study.

"If the adaptive trial is part of the initial plan of development, then the agency can provide a regulatory structure that would be necessary to review the results," Dr. Mills says.

WYETH

WE THINK OF THE PROCESS AS ADAPTIVE RESOURCE ALLOCATION, SO IF THERE IS A PROJECT THAT DESERVES HAVING MORE RESOURCES PUMPED INTO IT, WE MAY WANT TO DO SO AND EVEN INTENSIFY THE RESOURCES ALLOCATED TO THE PROJECT.

REGULATORY EFFORTS

The FDA already has issued guidelines for using adaptive designs for trials of medical devices. Issued in May 2006, this draft guidance provides the FDA's recommendations on the use of Bayesian statistical methods in the design and analysis of medical device trials.

In March 2006, the European Medicines Evaluation Agency (EMEA) issued a document that outlines some general considerations for studies with planned interim analyses. It doesn't discuss specific statistical methods but focuses on the opportunities for interim trial design modifications, and the prerequisites, problems, and pitfalls that must be considered.

In March 2007, a report from the EMEA/CHMP (Committee for Medicinal Products for Human Use) Think Tank Group on Innovative Drug Development recommended that the European agency issue a guideline on flexible design, as well as develop workshops specifically addressing the use of Bayesian methodology in confirmatory trials.

CHALLENGES OF ADAPTIVE DESIGN

Experts interviewed say one of the biggest challenges for using adaptive trials is cultural.

"Using adaptive designs is a new approach and our customers seem to be a little bit unsure about how this changes the way they work, the way they run trials, and the way they look at data," says Christian Marcazzo, senior director of life sciences at Spotfire Inc. "Many pharmaceutical companies have built their whole workflow in clinical research around the way things have been done for the past 15 years. Adaptive trials is one of many

things in the pharmaceutical industry that can be done better. But organizations, as a whole, struggle to change and shift to these new models because their standard operating procedures and the skill sets of the people who are working on clinical trials are geared around one particular way of working, one particular work flow, and one business model."

ETRIALS

AN ADAPTIVE DESIGN SHOULD NOT BE USED WHEN A COMPANY DOES NOT HAVE A PROCESS FOR CONDUCTING THE ADAPTIVE TRIAL, NOR WITH A NEW CHEMICAL ENTITY WHERE THERE IS NOT A LOT OF PREDICATE INFORMATION AVAILABLE.

CHRISTINE LYS

Experts say although there are many benefits to an adaptive trial design, this model shouldn't be used if the company has not set up a process for the new trial model or if there is not a lot of information already available.

"An adaptive trial basically involves creating a plan to modify the trial based on what is learned," says Christine Lys, M.S., director of business development at etrials Worldwide Inc. "If the compound is a new chemical entity or being investigated in a new therapeutic class where there is not a great deal known about the disease model, then how can we know what to adapt to?"

Dr. Collins says another challenge could be data management, cleaning the data, and making data available for analysis quickly.

"Speed is a critical success factor for adaptive designs," she says. "It is only when data management and data analysis can be managed quickly that companies can take advantage of adaptive designs. There is no fundamental reason that data cleaning should require more than a few days. To do this requires a well-designed and well-managed electronic data capture system."

Dr. Collins says achieving speed is not really a technology issue; it is a management issue.

"Sponsors cannot suddenly complete data management and statistical analysis for an adaptive trial in a few days if the process normally takes months," she says. "The database still has to be high quality. The technology to increase speed has been around for decades. Achieving change requires a particular management mindset either on the part of the sponsor or by the CRO."

Ms. Lys points out that for adaptive designs to be successful, integrated technologies in real time are needed.

"It's not just about using electronic data capture instead of a paper process; it also involves incorporating ECG, lab data, patient reported outcome data, imaging, any external lab information, and whatever it may be that is part of the actual study design," she says. "To make adaptive trials successful, people need to be involved as stakeholders — especially the people who are interpreting the data

THE SYSTEMS THAT ENABLE AN ADAPTIVE APPROACH

The true test of the suitability of data collection and processing systems for adaptive studies is more than a measure of discrete activities at the input stage, says Michael Rosenberg, M.D., MPH, CEO of Health Decisions.

Adaptive research is critically dependent on the timely availability of clean data and metadata for both strategic (design) and tactical (study management) decisions that determine the course of the trial. The more and sooner clean data and performance metrics are available, the greater the likelihood of making the right decision — especially if there is only one chance to make the decision, as in the case of an interim analysis. Conversely, delays in the availability of clean data can lead to less sure and possibly erroneous decisions and compromise other study activities, such as timely enrollment. The adaptive requirement for timely, clean data focuses attention on EDC systems because "electronic" is equated with "fast and accurate." While Web-based EDC systems are indeed faster than the laborious paper and hand entry-verification systems, they nevertheless remain considerably slower and less accurate than other EDC systems, such as the electronic pen, that do not require keyboard entry at the site and multiple transcription steps of data (source to CRF to keyboard).

A major deficiency in most Web-based EDC is that it deals solely with data, overlooking the more important ability to collect study performance metrics that provide the critical ability to effectively manage complex studies.

Adaptive research increasingly calls on systems that go beyond data capture for high-velocity programs. The "middleware" that turns data and metadata must effectively and promptly turn a stream of raw data into meaningful, actionable information that must be provided in different forms for different roles. This leads to further improvements in the research process, such as adaptive monitoring — monitoring according to need rather than rigid fixed schedules — and, more critically, the ability to look further ahead in the program to minimize the between-study intervals.

With experience on more than 300 adaptive trials, it's clear that data capture is necessary but not sufficient to run fast-moving programs. Indeed, the more important elements are performance metrics that enable the capability that lies at the heart of adaptive trials: continuous fine tuning of multiple study parameters. Even effective management of study supplies can affect key elements that underlie adaptive strategies, for example, if the right drug isn't at the right place when needed. This emphasizes the need for a fully integrated system that deals with data collection, randomization, data management, and logistics, such as supplies and payments.

The true test of the suitability of data collection and processing systems for adaptive studies is more than a measure of discrete activities at the input stage. Study decision-makers on multiple levels must have the timely, accurate information they need when they need it to make decisions based on adaptive criteria. A weak link anywhere along the chain will compromise the capability of the whole system and undermine the success of any of the adaptive components.

Source: Michael Rosenberg, M.D., MPH, CEO, Health Decisions Inc., Chapel Hill, N.C.
For more information, visit healthdec.com.

DR. BRIAN SCHWARTZ

ZIOPHARM ONCOLOGY

ADAPTIVE DESIGNS ARE VERY LABOR INTENSIVE BECAUSE DATA COLLECTION IS OCCURRING IN REAL TIME AND RESPONSES ARE HAPPENING IN REAL TIME.

CHRISTIAN MARCAZZO

SPOTFIRE

ORGANIZATIONS ARE STRUGGLING TO CHANGE AND SHIFT TO NEW MODELS BECAUSE STANDARD OPERATING PROCEDURES AND THE SKILL SETS OF PEOPLE WORKING ON CLINICAL TRIALS ARE GEARED AROUND ONE PARTICULAR WORK FLOW AND BUSINESS MODEL.

(the statistician and the clinicians). People also need to be involved up front so they can plan how they are going to get the data. Success is about process, technology, and the integration of stakeholders."

Adaptive designs are very labor intensive because of the need to collect data in real time, says Brian Schwartz, M.D., senior VP of medical and regulatory, and chief medical officer at Ziopharm Oncology Inc.

Executives at Ziopharm Oncology are evaluating adaptive designs and plan to implement these sometime in the next 18 months.

"It is very expensive to collect data in real time even though most computer systems can accommodate this," Dr. Schwartz says. "Another issue is that coordination is required for all the teams that participate in the process. This requires the integration of biostatistics, clinical, data management, clinical operations, drug supply, IT, and regulatory."

Planning and coordination of the process are essential, Dr. Schindler says.

"Each group needs to understand not just what it needs to do, but also what all the other groups will be doing and when," he says. "Once each group understands how its activities fit into the entire process, the adaptive trial can be managed. It's also important to allow extra time at the beginning for simulation to make sure that the adaptive design is appropriate."

Experts interviewed for this article say there is a need for guidance from the FDA.

Robert O'Neill, Ph.D., director of the Office of Biostatistics at the Center for Drug Evaluation and Research, FDA, says regulatory authorities are working on a guidance document, which should be available for public comment toward the end of 2008.

In the meantime, he suggests that sponsors contact individual medical divisions about any plans for adaptive trials.

"The FDA has begun to engage in exploring the value added by the use of these study designs and the opportunities they present, but we need to be very careful that these designs do not adversely impact the integrity of the clinical trial for regulatory purposes," he says.

Dr. O'Neill says one of the positives coming from these conversations has been a greater emphasis on better up-front prospective planning.

"We are likely to see more adaptation of designs in the learning phase of development, which I think can add value and which has not been traditionally the style of the industry," he says. "With regard to the use of adaptive designs in confirmatory, later-stage development, there is recognition that there are limited circumstances in which these designs could improve the efficiency as well as the success rate. There have been a lot of discussions, but not a whole lot of success stories yet."

INDUSTRY **PERSPECTIVE**

The Pharmaceutical Research and Manufacturers of America (PhRMA) also has been working for some time to address issues around adaptive designs. PhRMA formed a Working Group on Adaptive Designs in March 2005, which aims to contribute to a

DR. GEORGE MILLS

PAREXEL

AT THE PRESENT TIME, ADAPTIVE DESIGNS ARE BEING CONSIDERED FIRST FOR EARLY-STAGE TRIALS AND WON'T BE APPLIED IN LATE-STAGE CLINICAL TRIALS UNTIL THE RAMIFICATIONS ARE FULLY UNDERSTOOD.

dialogue on adaptive designs by engaging statisticians, clinicians, and other stakeholders in academia, regulatory agencies, and the industry.

At Wyeth, the processes put in place to evaluate adaptive designs have become a tool to improve the way the company does business, says Michael Krams, Ph.D., assistant VP of adaptive trials and head of the Learn and Confirm Adaptive Trials team at Wyeth Research & Development.

"We look at adaptive trials as a pivotal point to integrate Critical Path opportunities, such as biomarkers and study design, but also take into account other utilities such as drug supply management," he says. "At any point we ask: how can we most efficiently increase our confidence level to continue investing into a particular asset?"

He says the company looks at the process as adaptive resource allocation.

"If there is a project that deserves to have more resources, we may want to intensify the resources allocated to the project," Dr. Krams says. "But if there is a project that doesn't deserve the resources then we can withdraw them in a timely fashion."

Dr. Schindler says Merck has learned that it's best to begin early in the drug-development process when planning to use an adaptive design.

"An adaptive dose response trial is a good place to start for the first adaptive trial," he says. "Concerns about introducing bias are

Sound Bites from the Field

PHARMAVOICE ASKED EXPERTS TO DEFINE ADAPTIVE TRIALS AND HOW TO PUT THESE DESIGNS INTO PRACTICE.

PHILLIP L. BANKS, MS, FRS, is Senior Director of Biostatistics and Information Technology of Prologue Research Inc., Columbus, Ohio, which is a global oncology contract research organization that offers a full range of clinical research services for Phase I-IV international or U.S.-based clinical trials in oncology and oncology-related studies. For more information, visit procro.com.

"The primary objective of an adaptive trial is to modify a study design based on interim looks at observed data with adequate control of the Type I error, for example, probability of concluding that a treatment difference exists when, in fact, it does not. Modifications can be made for a number of design features and include: re-estimating the sample size, changing the treatment arm allocation ratio, eliminating/adding treatment arms, reformulating the study hypothesis, and enriching subpopulations.

Adaptive trials can aid the drug-development process by requiring fewer patients and/or a reduced time to meet study endpoints. But these designs can result in complicated decisions and uncertainty about the best approach for data analysis. In planning an adaptive trial, one needs to preserve the operational characteristics of the design and maintain credibility. Consequently, these trials require extensive planning and should be a collaborative effort with regulatory authorities."

HUGH LEVAUX is VP of Product Strategy of Medidata Solutions Worldwide, New York, which helps the world's leading pharmaceutical, biotechnology, medical-device, and research organizations maximize the value of their clinical research investments. For more information, visit mdsol.com.

"A study design is adaptive if it allows for the modification of an essential design feature based on the results of data collected and analyzed at predetermined intervals during that trial. A flexible and integrated electronic data capture (EDC) and clinical data management system allows for early visibility into trial data, which enables researchers to analyze data and make critical decisions about potential adjustments to trial sample size, treatment and dosage allocation, and/or inclusion/exclusion criteria.

This review enables researchers to eliminate futile doses or arms, focusing the data collection on dosage combinations yielding best efficacy and safety to improve the ethics, science, and efficiency of clinical trials."

MARK WAXMAN is a Partner at Foley & Lardner LLP, Boston, a law firm that provides a full range of corporate legal counsel. For more information, visit foley.com.

"If a company could apply decision making to the trial as it goes along, it could either terminate the trial, change it, or get it more focused on what the actual end point is. There is a desire to make these trials more efficient. There are going to be a lot of questions about adaptive designs. Creating bias in favor of positive results is one issue.

The goal of some of these is to permit early stopping and resizing of samples and reestimation. There is always some type of risk associated with this approach; these trials are statistically driven and statistics are not guarantees.

One of the challenges is how an institutional review board (IRB) will look at these trials and approve them at the outset, which precludes having to have the sponsor come back to the IRB every time there's an adaptation.

Any material change in a trial requires sponsors to go back to the IRB to have a discussion about whether the design is appropriate and if patient has been fully informed and given consent."

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DR. SYLVA COLLINS

KENDLE

WITH COST PRESSURES ON THE PHARMA INDUSTRY, ADAPTIVE TRIAL DESIGN IS AN AREA WHERE THERE'S POTENTIAL FOR SIGNIFICANT COST SAVINGS AND COMPETITIVE ADVANTAGE FOR COMPANIES THAT CAN IMPLEMENT THIS MODEL.

DR. JERALD SCHINDLER

MERCK

ADAPTIVE TRIALS REQUIRE THE COORDINATION OF BIOSTATISTICS, CLINICAL, DATA MANAGEMENT, CLINICAL OPERATIONS, DRUG SUPPLY, IT, AND REGULATORY FUNCTIONS.

lower, and the total amount of data used in the adaptive analysis is less. Then, over time, we can increase the number of trials involving dose response and then even later the number of pivotal trials."

Dr. Krams says Wyeth has established predefined decision points for its drug development model.

"At some stage we will need to make the decision about whether we want to take the compound into a confirmatory drug development trial, which is expensive and time intensive," he says. "We look at these decision points and determine which research questions need to be addressed properly before we can make the decision. For instance, if we want to take a compound into the confirmatory development phase we may need to clearly understand the dose responses."

He says adaptive designs allow for improved learning about the dose-response and informed decision-making on which doses to take into confirmatory trials.

"We want to ensure that valuable new therapies come to market as soon as possible," Dr. Krams says. "We don't want to waste time. The contribution of the adaptive interface is to help us come to the correct decision at the earliest possible time point. The advantage of this approach is its flexibility. Traditionally, we make assumptions and then are locked into what we assumed, say for instance on the variability of a particular endpoint. But what if we got it wrong? The entire research effort might be wasted." ✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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