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WHITE PAPER

IMPLEMENTING ADAPTIVE TRIAL DESIGN:

OPERATIONAL CONSIDERATIONS AND THE ROLE OF THE CRO

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EXECUTIVE SUMMARY

Adaptive trial designs are gaining acceptance with both drug developers and regulators as a means to improve clinical trial efficiencies. Draft guidance from the U.S. Food and Drug Administration (FDA) now provides a regulatory framework that encourages sponsors to explore the benefits of adaptive designs. At the same time, technologies such as electronic data capture (EDC) and real-time data access are enabling adaptive study operations. Adaptive designs offer the potential to reduce timelines and patient exposure while increasing the potential for successful outcomes. But along with these benefits come challenges: additional complexity, needs for greater statistical expertise and increased operational demands. This paper discusses operational considerations posed by adaptive designs, particularly in global studies, and offers insights into the role of contract research organizations (CROs) in planning and execution.

INTRODUCTION

Adaptive trial design is a major advance in clinical trial methodology that allows for smaller, faster trials while ensuring scientific rigor and integrity of results. Adaptive approaches can also enable larger and longer studies—for example, by combining and streamlining research that would otherwise be conducted as two separate trials. Adaptive designs use accruing data to change the trial as research moves forward, leveraging early data to guide decisions that can accelerate timelines and reduce costs. Although adaptive designs offer persuasive benefits, some sponsors remain cautious about using the new approaches. This is changing, however, as growing experience and clearer regulatory guidance encourage expanded use of this emerging methodology.

Rigid vs. Flexible Design. In conventional designs, research progresses in a lock-step fashion. The trial is completed, results are analyzed and the compound is (or isn't) advanced to the next research phase. Decisions regarding dosage, randomization and sample size are made in advance and fixed throughout the study. Using this probabilistic statistical approach, studies have to be large to ensure statistical significance. Timelines run to years, often with millions of dollars invested and thousands of patients involved, before final results demonstrate success or failure.

In an adaptive trial, data are analyzed at designated interim points, allowing researchers to use results to focus the trial on the most promising doses, disease indications or patient populations. The study design is not fixed but rather is defined by available information as the trial proceeds. Using this adaptive approach, early findings can be used to redirect the trial toward the most positive outcomes—for example, by halting evaluation of a dose that interim analysis shows to be ineffective and reallocating those patients to an effective dose. This continuous, data-informed process increases the likelihood of success.

These benefits sparked interest in adaptive approaches in the early 2000s, but adaptive designs also posed concerns. Adaptive designs often use Bayesian statistical methodology and therefore require special expertise in this area. Adaptive studies also require additional planning and regulatory interaction. Current regulatory guidance documents identify concerns regarding the control of the type 1 error, potential for bias and issues related to unblinding, which is required at the interim analysis for some designs. Analysts also note a scarcity of expertise with adaptive trials, but experience with and regulatory acceptance of adaptive approaches are increasing.

EVOLVING REGULATION: FDA'S 2010 DRAFT GUIDANCE

In 2006, the FDA issued a Critical Path Opportunities Report calling for the development of new adaptive design methods to increase trial efficiencies.[1] The FDA's critical path initiative promotes "model-based drug development," which advances research by applying early data to improve decision-making. Adaptive designs promised to improve efficiencies in Phase I and Phase II, and provide more information to guide Phase III trials, in which failure rates approached 50 percent.

In 2006, the European Medicines Agency (EMA) issued a draft reflection paper titled *Methodological Issues in Confirmatory Clinical Trials with an Adaptive Design,* which was finalized in 2007.[2] This document provided the first regulatory guidance on adaptive design, and although it was an important and useful first step, its scope was limited to confirmatory trials. It acknowledged potential benefits of adaptive trials but its emphasis was on caution.

In 2010, the FDA issued a draft guidance, *Adaptive Clinical Trials for Drug and Biologics*.[3] The guidance defines an adaptive study as one that "includes a prospectively planned opportunity for modification of one or more specified aspect of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study." Analyses of accumulating trial data are conducted at planned timepoints and can be performed "in a fully blinded manner or in an unblinded manner." Noting that many design modifications are possible, the FDA guidance specifically mentions nine examples of possible adaptations, including eligibility criteria, randomization procedure, primary endpoints, treatment regimens of study groups based on dose, schedule and duration, and total sample size including early termination.

Well-Established and Less-Familiar Designs. The draft recognizes two categories of adaptive designs: familiar designs that represent well-established and relatively low-risk approaches to enhance study efficiency and informativeness; and less familiar designs that are not yet well established in drug development and may pose risks to study validity and interpretation.

Well-established designs. The guidance cites five familiar, relatively low-risk designs that "may deserve wider use":

- Adaptations of study eligibility criteria based on analyses of pretreatment (baseline) data
- Adaptations to maintain study power, based on blinded interim analyses of aggregate data
- Adaptations based on interim results of an outcome not related to efficacy
- Adaptations to enable early study termination due to lack of benefit or efficacy
- Adaptations in the Data Analysis Plan that don't depend on within-study or between-group outcome differences

Less-familiar designs. Because these approaches are less well understood, the FDA recommends caution when using them in confirmatory trials but encourages their use in exploratory trials. The agency considers them promising and anticipates wider use as knowledge grows concerning their appropriate application, benefits and risks:

- Adaptation for dose selections studies
- Adaptive randomization based on relative treatment group responses
- Adaptations of sample size based on interim-effect size estimates
- Adaptation of patient population based on estimates of treatment effect
- Adaptation for endpoint selection based on interim estimate of treatment effect
- Adaptation of multiple-study design features in a single study
- Adaptations in non-inferiority studies

CURRENT PRACTICE

There are few measures of the use of adaptive designs in clinical trials, but adoption is clearly increasing. By 2002, adaptive designs had been used in only 46 studies reviewed by the FDA in regulatory submissions.[4] In a 2011 survey of 30 biostatisticians and product development executives in biopharmaceutical companies and clinical research firms, 75 percent reported they had conducted or considered conducting an adaptive study. The survey, conducted by Elsevier Business Intelligence, also found that among this group, 85 percent had designed or conducted fewer than five adaptive trials.[5]

Most Common Designs. Many sponsors are focusing their resources on simpler designs in efforts to reduce time and cost while avoiding risks posed by more complex approaches. Several types of adaptive design especially suit this profile:

Adaptation for dose response estimation. In conventional Phase II trials, two or three different doses are usually evaluated, and the best dose is selected for use in Phase III. This approach is limited, since it is not known if the best of the doses tried is the optimal dose. Adaptive designs can evaluate a wider range of doses, gradually eliminating the worst and focusing on the most promising. This increases likelihood of identifying the optimal dose for use in Phase III.

Adaptation for sample size re-estimation. In conventional trials, sample size is based on initial assumptions about primary efficacy parameters (including variability and clinically relevant differences) and the rate and timing of patient withdrawal. The sample size is calculated early and remains fixed. This can result in an under-powered study that does not show clear-cut results. Using adaptive design, sample size can be re-estimated based on early data, and study size can be increased to ensure adequate powering.

Adaptation of patient population. Early information on patient outcomes also allows identification of sub-groups in which the drug may work especially well or poorly. Recruitment can be halted for patients unlikely to benefit and then be redirected to enroll patients most likely to experience effectiveness.

Adaptation to terminate early due to lack of efficacy. The FDA's 2004 report on critical path opportunities cited the need to reduce costly development failures: "A 10 percent improvement in predicting failures before clinical trials could save $100 million in development costs per drug."[6] Adaptive designs enable early halts based on interim analyses that demonstrate lack of utility. Early stops can save the cost of an entire program which, conducted under a conventional design, would have to be completed before lack of utility was determined. It is worth noting that this type of adaptive design falls into the framework of Group Sequential Designs, which have been used within the biopharmaceutical industry for more than 20 years and pre-date the term "adaptive" design.

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Benefits. The use of accruing data in adaptive designs can reduce patient exposure, increase chances of identifying the optimal dose and reduce study size and timelines. Adaptive studies are particularly suitable in therapeutic areas such as oncology, in which efficacy and safety must be evaluated in many potential indications and disease stages. Economic benefits are difficult to measure and are most likely to be seen over the course of a full development program rather than in a single trial. Anecdotal estimates suggest potential development cost savings in the range of 20 to 30 percent. In a recent industry presentation, a major pharmaceutical company representative commented that adaptive designs were saving the company tens of millions of dollars annually.[7] Overall, these flexible, learn-and-confirm approaches enhance knowledge of drug effects and increase likelihood of successful trials.

Challenges and Risks. Sponsors face challenges in implementing these new approaches. Adaptive trials are more complex than conventional designs, and they require additional planning, regulatory consultation and technology capabilities to support efficient interim analysis. Expertise and experience in developing and executing adaptive studies is increasing but still limited overall.

Regulatory considerations. Although regulators encourage adaptive designs, they also have valid concerns regarding the potential for bias—that is, that adaptive design could result in different results compared to a conventional design. Regulators generally have fewer concerns about

adaptations in Phase I and Phase II studies. However, there is still serious regulatory concern about the use of certain adaptive designs in pivotal Phase III trials. When sponsors are considering adaptive Phase III studies, it is essential to open discussions early and confirm acceptance of the approach with the FDA and EMA. Special protocol assessments entail timelines (45-day responses) and commitments that may not be best suited for adaptive studies. The full review and assessment of a study using adaptive design methods can be complex, will involve multidisciplinary evaluation teams and may involve extended discussions among regulators in different FDA offices before reaching a conclusion.

Planning and simulation. Adaptive trials take longer to design. As a result, sponsors will need more time to consider the implications of making changes to a trial in midcourse. The FDA expects to see simulations that predict likely outcomes, and modeling and simulation requires additional time and expertise.

Unblinding. Interim analysis must be conducted by, and results seen by, only a small number of people not involved in direct conduct of the study. Unblinding practice must be planned and conducted in a carefully controlled manner.

Infrastructure. Adaptive designs depend on interim data and require infrastructure that allows for rapid data cleaning and analysis so that timely results based on correct data are available for key data points at designated timepoints.

THE ROLE OF THE CRO

At present, there are a number of CROs—both major and niche providers—that can offer expertise and experience in statistical methodology, regulatory affairs and trial conduct. When selecting a CRO, sponsors should seek a provider with in-depth understanding of adaptive design and logistics, with capability to work across disciplines and with the operational infrastructure necessary to support adaptive study execution.

Essential Expertise. Biostatisticians need expertise and experience in adaptive trial design methodology and benefit from experience in Bayesian methodology. Capability is also needed to support modeling and simulations to predict likely outcomes of trial adaptations. To implement adaptive approaches, teams need to work across disciplines to anticipate and address changes in trial design as research moves forward.

Strong Project Management. Strong project management is required to identify key study criteria and potential risks and to provide mitigation strategies early in the course of the study. Project managers must be able to deal with the additional complexity of adaptive trials and to facilitate close collaborations and coordination among different functional departments and operational groups during the course of the study—particularly during the time of any interim analyses.

Electronic Technology Platform. Achieving the benefits of adaptive studies requires effective use of electronic technology, including electronic data capture (EDC) and real-time data access. To shape trials based on interim results, data must be collected, monitored, cleaned and analyzed quickly, accurately and reliably. EDC eliminates time-consuming tasks, such as collection and processing data from case report forms (CRFs). Real-time access speeds data cleaning and analysis. Capabilities for electronic data integration are critical to speed access to multiple data streams, such as interactive voice response system (IVRS) data and laboratory results. Real-time, integrated data also gives research teams the ability to monitor data on an ongoing basis across interim timepoints—a concept that is gaining momentum, particularly as a means to monitor safety.

Confidentiality. The CRO needs to be able to maintain confidentiality of the information examined in the interim analysis. The ability for the FDA to verify compliance, potentially by on-site auditing, may be critical.

Simulation Software. The FDA asks to review simulation data in advance of adaptive trials. Simulations generate scenarios that predict likely outcomes of various design options to alert researchers to possible outcomes and help prepare for decisions downstream. Several software companies have developed software to simulate designs and check the ability of study designs to maintain power and control the Type 1 error.

Figure 1, on page 9, shows an example of different simulation scenarios and evaluation of their operating characteristics.

OPERATIONAL CONSIDERATIONS: RATIONALE, SITE ISSUES, GLOBAL CHALLENGES

When considering an adaptive study, sponsors should keep in mind a number of operational issues that will impact the conduct of the trial. Adaptive design may or may not be the optimal approach for a given study. There will be special demands on site operations. And in global studies, there is the additional challenge of multiple regulatory venues.

Rationale for Using Adaptive Designs. Is adaptive design the right choice for a given study? In principle, all trials can benefit from adaptive approaches. In practice, operational benefits are greater in some studies than in others. Sponsors need to determine whether study characteristics are amenable to an adaptive design.

Short-term endpoints. Availability of short-term endpoints with a strong correlation between interim results and final study outcomes greatly facilitate the use of adaptive designs. For example, a strongly correlated biomarker will enable an early interim analysis, whereas an interim analysis for a long-term endpoint, such as two-year overall survival, will take considerably longer. However, the interim analysis using a biomarker will only be predictive if there is a correlation between the two.

Therapeutic indication. Adaptive designs offer greater benefits—particularly in acquiring information to support go/no-go decisions and early termination—in therapeutic areas such as oncology that have relatively high failure rates. In PPD's experience, most adaptive trials have been conducted in oncology; sponsors can expect more experience in this arena to guide operational decisions and anticipate regulatory expectations.

FIGURE 1: SIX SIMULATION SCENARIOS

Figure 1 displays the potential pattern of a response variable (in this case a dose limiting toxicity – DLT) for four different dose levels. Six different simulation scenarios are explored, ranging from all dose levels being very safe (with very low probability for a DLT, Scenario 1) to all of them being unsafe (with high probability of a DLT, which is also increasing by dose level, Scenario 6).

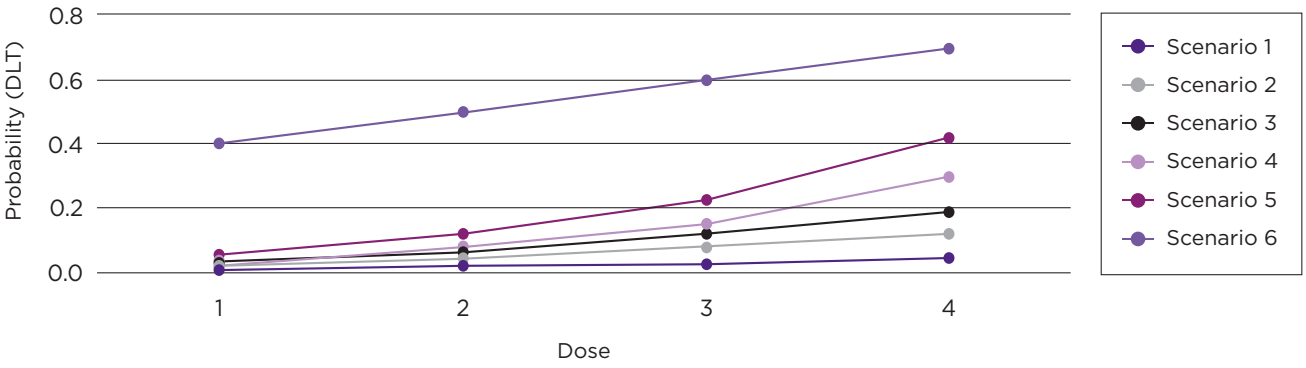

TABLE 1: THE OPERATING CHARACTERISTICS FOR SCENARIO 4

Table 1 shows the operating characteristics for one of the simulation scenarios (Scenario 4). It displays the mean sample size for each of the four dose levels (where two different dose schedules are also investigated for each dose level), together with the associated variability (SD), as well as overall. The last column displays the probability that the relevant regimen is chosen as the Maximum Tolerated Dose (MTD).

DOSE LEVEL	SCHEDULE	TRUE DLT RATE	MEAN N	SD N	PR(MTD)
1	Option A	0.03	2.1	1.9	0.054
1	Option B	0.03	0.7	1.6	0.023
2	Option A	0.08	3.1	1.9	0.286
2	Option B	0.08	3.1	2.9	0.288
3	Option A	0.15	2.1	1.1	0.334
3	Option B	0.15	3.5	2.3	0.417
4	Option A	0.30	4.6	3.2	0.324
4	Option B	0.30	3.3	3.3	0.270
Experimental			22.5	1.8	
Control			14.3	0.9	

Site Considerations: Recruitment and Timely Data Collection. Conventional studies focus on rapid patient enrollment to speed study start-up. But in adaptive studies, slow initial recruitment is sometimes better, as it allows for changes. Interim results can direct recruitment toward specific patient sub-groups most likely to experience benefit, or away from patients likely to suffer adverse effects. Study sites must be especially vigilant to avoid delays that impact interim analyses. In conventional studies, delay in a patient visit is a minor issue; in an adaptive trial, a missed or late patient visit can be a major barrier to meeting interim deadlines.

Challenges in Global Trials. The size and complexity of global trials add to the challenges of analyzing interim data quickly and accurately, and varying regulatory and treatment environments can be extremely difficult to navigate.

Site monitoring. Site monitors need special awareness to meet the exact interim analyses requirements and to manage data collection operations likely to cause delays. For example, laboratory samples pose special concerns, since they must be shipped to central locations for analysis. Real-time, integrated data platforms are critical to resolve data queries quickly and deliver interim results at required timepoints.

Standards of care. Sponsors need to be aware of varying standards of care and how differences will impact adaptive studies conducted in multiple countries. As in all trials, it is critical to identify appropriate patients and their differences across regions, and to understand how these differences will impact overall results. In adaptive trials, these differences may affect decisions made to study design at interim analysis. If not taken into account, they can lead to inappropriate design adaptations.

Regulatory considerations. Regulation pertaining to adaptive design varies from country to country. At present, the FDA and EMA are the only agencies that provide regulatory guidance. In the conduct of global studies, sponsors must operate in the context of a wide range of regulatory experience and expectation. For pivotal trials, sponsors need to confirm regulatory acceptance in each country where a license application will be submitted. Global regulatory expertise is necessary to build relationships with various regulatory agencies and navigate procedures for consultation.

THE FUTURE OF ADAPTIVE DESIGN

It is clear that adaptive design offers one of the best opportunities to advance knowledge and efficiency in clinical research. Although experience is increasing, many drug developers remain cautious in their applications, and it will take time for regulators and the industry to understand the benefits in the context of the greater demands adaptive approaches place on planning and operations. To realize its full potential, adaptive design will have to prove its benefits in global studies, where the operational and regulatory hurdles are especially high.

Adoption of this valuable new tool will be driven by the urgent need to reduce the time and cost of drug development. At present, the most compelling benefit of adaptive trial design is the ability to halt failures early, and the immediate growth area is in clinical evaluation of oncology agents, which comprise nearly half of today's development pipeline. The publication of the FDA's final adaptive design guidance is likely to further accelerate the use of adaptive design in clinical development.

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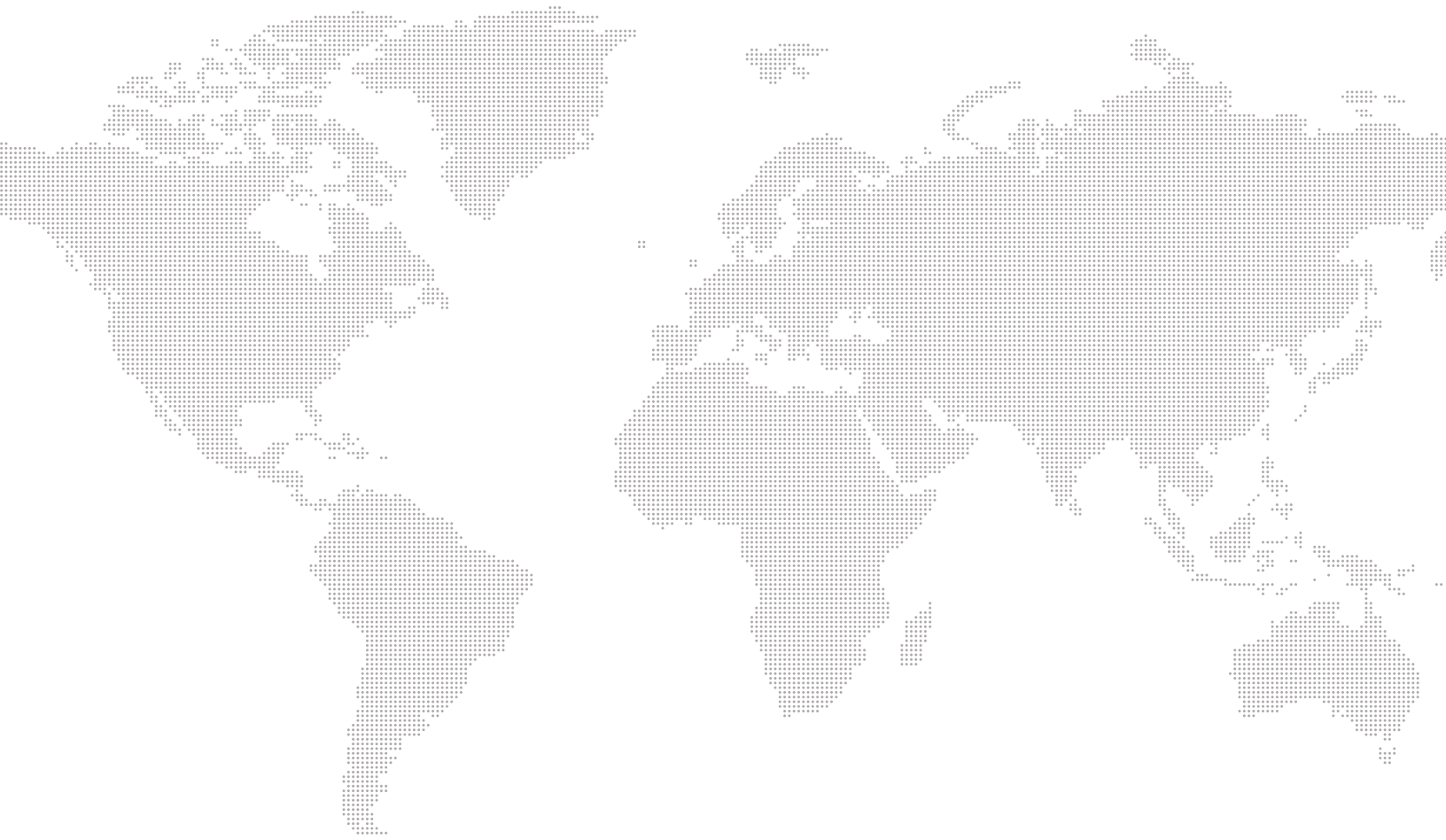

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