ADAPTIVE TRIAL DESIGNS:

IMPROVING THE EFFICIENCY OF DRUG DEVELOPMENT

Partnering with Covance gives you a head start on designing and executing adaptive clinical trials

Eric Lang, MD
Vice President and Global Head of Clinical Development Leaders, Early Phase Development Solutions

There is a growing concern—among regulators, biopharmaceutical companies and CROs—that the productivity rate of drug development continues to fall. Clinical trial efficiency, or the lack thereof, is at the root of the problem. The oft-quoted figure that only 50% of drugs entering Phase III are successful in attaining FDA approval needs to be improved, pointing to the question of predictability. Additionally, the cost of individual trials continues to increase, raising the question of clinical trial efficiency. This is not just an issue in the confirm phase—efficiency in the learn phase can benefit industry by helping to:

- Find the right dose-response curve and the right population
- Better protect patients
- Test multiple compounds in a single master trial—the master protocol
- Inform better decisions

One way to improve both predictability and efficiency that has been gaining considerable momentum in the last few years is the increased use of adaptive trial designs. Compared to traditional trials, adaptive clinical trials are generally more efficient—using fewer patients and/or less time, subjecting fewer patients to potentially harmful compounds and resulting in more information per dollar of investment.

The advantages that sophisticated adaptive trial *designs* have in efficiently running clinical trials have been discussed in the scientific community—principally in the statistical area—for many years. However, until recently there has been little focus on the requirements to *execute* an adaptive clinical trial. Recent gains in technology, statistical methodology and techniques, and increases in the number of clinical trial professionals with experience in executing adaptive trials, have brought significant advances.

The increased efficiency of adaptive trial designs comes at a price because the operational infrastructure and procedures can be more complex than in a traditional trial. These concerns involve ensuring trial integrity and trial validity. Integrity refers to ensuring that proper pre-planning based on intended adaptations has occurred and that the confidentiality of data is maintained throughout the trial and operational bias is minimized. Validity refers to providing correct statistical inference (such as adjusted p-values, estimates and confidence intervals), while assuring consistency between different stages of the study. You need a partner that can address both of these throughout a trial.

COVANCE®
SOLUTIONS MADE REAL®

A Note on Nomenclature

Within the biopharmaceutical industry, a broader term of adaptive trial is sometimes used, and this includes the observation that most trials have protocol amendments that are enacted during the course of the trial. These protocol amendments attempt to fix errors or wrong assumptions in the original protocol. They are not (or should not) be based on any of the specific efficacy data (especially unblinded data) that are accumulated during the trial. The Statistical Analysis Plan (SAP) may be adjusted during the trial to reflect new information that is available or new thoughts on how to present the data. Both protocol amendments and modifications of the SAP are *not* part of what is commonly termed an adaptive trial design.

Some people say that adaptive trials are no different than any other clinical trial, that there are always modifications made. The difference is that in an adaptive trial design the changes are pre-specified in the protocol—agreed upon with regulatory authorities before the trial begins—and very careful attention is paid to maintaining statistical validity and trial integrity through defined statistical and procedural approaches. This contrasts sharply with a "traditional" clinical trial approach that fixes the study design and hypothesis at the beginning and does not take into account accumulating data during the trial.

A second area of confusion is the term "adaptive monitoring." Adaptive monitoring is often used in relation to risk-based monitoring or to show the flexibility of an organization's approach on how to monitor clinical trials. It is not adaptive clinical design or execution. Adaptive monitoring may be used in an adaptive clinical trial, but only as a way of facilitating and making the actual clinical monitoring of a trial more efficient. It is *not* related to adaptive design. It does contribute, however, to the efficiency of a trial (i.e., decreasing cost).

Industry Acceptance and Market Penetration

Adaptive trial designs are of growing interest to our biopharmaceutical clients. A recent paper from the Tufts Center for Drug Development[1] estimated that simple adaptive designs today are used on approximately 20% of clinical trials. This figure is similar to that found in recent primary market research conducted by Covance. Importantly, our survey results also support findings in other publications that approximately 35% - 45% of trials in Phase Ib - Phase III *would consider* an adaptive design in the final study protocol.

There is a larger market opportunity in the learn phase than in the confirm phase; however, growth in the confirm phase is anticipated to accelerate in the future. The majority of the adaptive design trials today could be classified as simple based on their statistical complexity (Table 1). However, one of the key aspects of adaptive design and execution is the complexity of the operational infrastructure that is required to efficiently and effectively run adaptive clinical trials. This depends on, among other things, the number of times that adaptations are run, the frequency with which they are run, the number of adaptations that are part of the adaptive design and the general familiarity with the type of design by both sponsors and regulators.

Table 1: Types of Adaptive Designs Based On Statistical Complexity

Simple Designs	Usage
Group sequential (blinded)	Phase II/III
Sample size re-estimation (blinded)	Phase II/III
Adaptations unrelated to efficacy	Phase II/III
Continual Reassessment Method (CRM)	Phase I
Complex Designs	
Adaptive dose-finding	Phase I
Adaptive group sequential design	Phase II/III
Sample size re-estimation (unblinded)	Phase II/III
Adaptive randomization	Phase II
Drop underperforming treatment arms	Phase II
Adaptive hypothesis design	Phase II/III
Seamless Phase I/II	Phase I/II
Seamless Phase II/III	Phase II/III
Population enrichment	Phase III
Multiple adaptive design	Phase II
Master protocols	Phase II/III

[1] Kenneth I Kaitin, PhD, "The Adoption and Impact of Adaptive Trial Designs," Tufts Center for the Study of Drug Development Senior Leadership Brief (2013)

COVANCE®
SOLUTIONS MADE REAL®

The ability to design clinical trials differently to address both efficiency and predictability exists today, primarily through adaptive trial designs. However, other methodologies such as MCP-MOD can be very valuable in the right context.

Characteristics of Ideal Candidates for Adaptive Trials

Adaptive designs are not for all compounds. There are several considerations to determine whether an adaptive design is right for a trial on a particular compound. From a high level, the key to adaptive design is that it has accumulating data throughout a trial on which decisions can be made. The main factors important in assessing whether an adaptive trial is appropriate for a specific compound are listed below.

- Substantial uncertainty around key trial parameters (population variance, effect size, treatment, appropriate dose, etc.)
- Biomarker/surrogate predicator relationship to actual clinical effect is well understood
- Ability to quickly measure the clinical efficacy (either directly or through readouts from biomarkers)
- Recruitment speed relative to measuring the clinical effect is in line with ability to make adaptation decisions
- Relationship of logistical (operational) costs to benefits from using adaptive designs is reasonable and well understood
- Cost of potential increased drug supply wastage versus a traditional trial are not excessive
- Candidates for which specific ethical issues can be important (e.g., long trials with significant uncertainty in key parameters)
- Compounds in the learn phase (Phases I and II) are more favored by regulators as there is faster regulatory acceptance and the hurdles of the confirmatory process are not encountered
- Designs with only limited number of adaptations are preferred, as sponsors may face higher regulatory hurdles with multiple adaptations
- With Bayesian approach, quality of prior information is good—if prior information is not good, Bayesian approach will result in wrong starting points and a loss of efficiency
- Studies utilizing well-performing sites with strong history of providing clean data (in order to minimize query rates) and speed accurate and timely information collection

The Covance Approach

An innovative development approach may require an adaptive trial design and the partnership of a global CRO. With a presence in more than 60 countries, Covance has helped pharmaceutical and biotech companies develop 100% of the Top 50 best selling drugs on the market today. We approach adaptive trial design at both the design and execution level by leveraging integrated processes, advanced technology and a core team of highly trained individuals across biostatistics, project management, medical and regulatory affairs who are versed in designing and conducting adaptive clinical trials.

Eric Lang, MD

Dr. Lang has more than 17 years of experience in drug development in the pharmaceutical industry in both large and small pharma. His experience includes leading drug development teams that have successfully filed NDAs; directing clinical operations, clinical development and pharmaceutical business development; and designing, planning and directing regulatory strategies. Dr. Lang has negotiated with the FDA regarding clinical and regulatory development programs for drug and device approvals.

Learn more about our drug development solutions at **www.covance.com**

The Americas + 1.888.COVANCE + 1.609.452.4440
Europe / Africa + 00.800.2682.2682 **Asia Pacific** + 800.6568.3000

COVANCE®
SOLUTIONS MADE REAL®