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Trial Design



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Dissecting Adaptive Design

Team and technology benefits are realized at the front-end of the adaptive trial design process.

Adaptive or flexible trial design refers to a conceptual clinical trial methodology that allows for modifications to take place after the trial has started without compromising the scientific method. For all forms of adaptive design, the important distinction that is critical to maintaining the research perspective is that the decision-making rules governing the adaptation must be clearly stated (described and justified) in the study protocol.

In an adaptive design setting, sponsors are empowered to make modifications in response to data collected during the trial as long as the

response action and decision-making rules are pre-defined. These Scientific Study Modification Points (SSMPs) can occur frequently (in a fully sequential design) or at other predetermined intervals.

Adaptive trials by design have midstudy analysis and decision points that will change the way a study is conducted. As adaptive trial methodologies are relatively new to most pharmaceutical and biotech companies and their vendors, there is the potential that midstudy modifications to the study design could have a negative impact on the clinical trial if not properly executed.

Kesler and Helms summarized some of the logistical and technological needs of adaptive trial designs well,¹ including the need to access clean study data as quickly as possible to make trial decisions. Adaptive studies require central, adaptable randomizations (either IVRS or Web-based); the ability to stop randomization quickly; and the ability to mask pruning of treatment arms from sites. Adaptive trial design also requires expe-

It is critical that all downstream teams are involved in early development.

ditioned monitoring to get the most data available for the interim analyses. The team should also have analysis programs ready in order to display interim results quickly.

Trial necessities

The communication and teamwork required for adaptive trials are very different than the linear approach taken in traditional trials (See Figure 1). In an adaptive trial, communication requires that team members are brought together earlier and more often throughout the trial (see Figure 2). The members need to be involved at the SSMPs to analyze the impact of modifications to their areas of study conduct. Once analyzed and decisions made, the predetermined logistics required will be executed by the team members and/or automated systems.

Also in an adaptive trial setting, a monitoring board might

have the option of responding to interim safety and efficacy data. These data may come from the trial itself or other new information in the drug development process that was not available at study's start. The Independent Safety and Monitoring Board can respond to the new information in a number of different ways, including narrowing the trial focus or increasing the patient population. An example of narrowing the trial focus might include removal of one or more of the treatment arms based on predetermined futility rules. Alternatively, if the data available at the time of the review does not allow for a clear decision between utility and futility, it might be decided to expand the enrollment of patients on one or more treatment arms beyond the initially targeted sample size.

These options are available in an adaptive trial, unlike in a standard trial where safety and efficacy data may be reviewed by a monitoring board during scheduled interim analyses. The response to this data in a standard trial is generally either amending the protocol or stopping the trial and starting a new one. Either response is costly to timelines and budgets.

How Traditional Trials Approach Teamwork

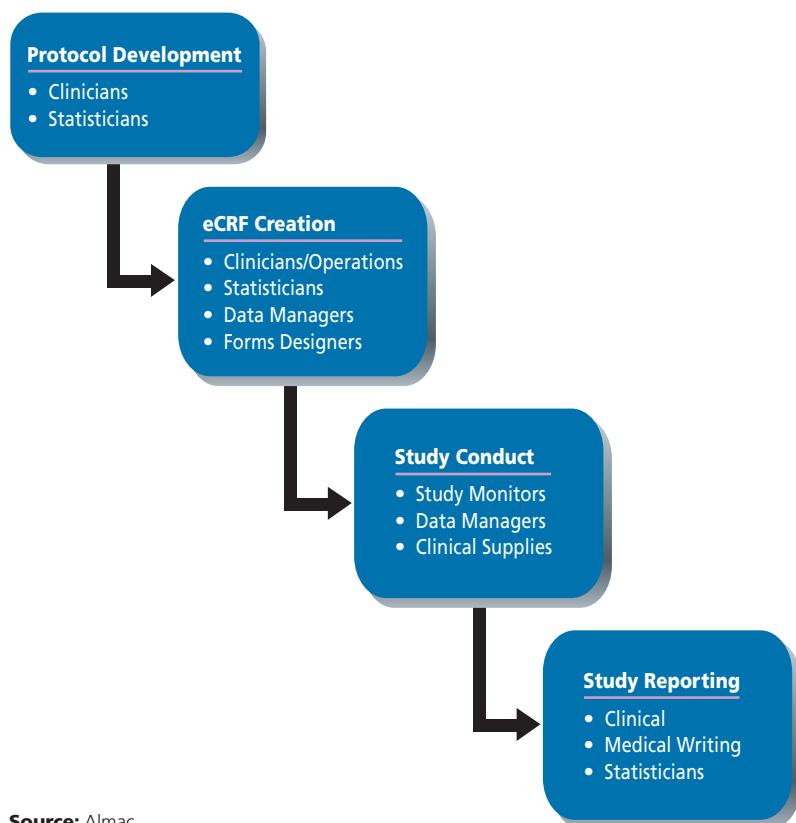


Figure 1. Linear hierarchy and stepwise communication characterize the traditional trial environment.

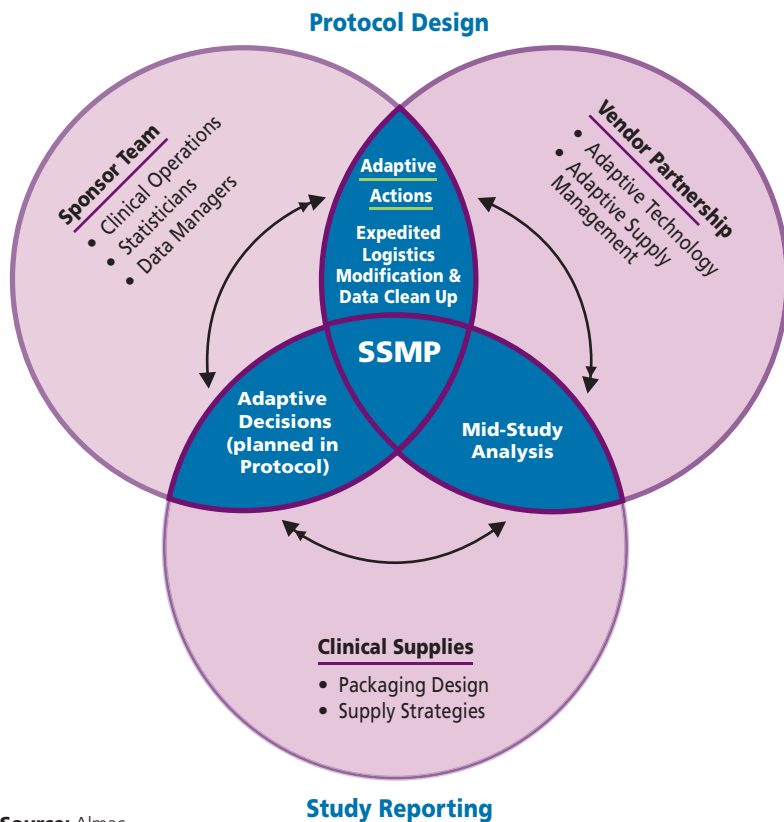
The adaptive environment

The adaptive trial environment is much different than the traditional trial environment, where hierarchy and stepwise communication is the norm. In an adaptive trial, the teams are interactive, synergistic, and highly engaged. This is necessary in order to respond to the SSMPs. Other characteristics of an adaptive clinical trial include the following:

Early planning with full scenario development. Very early in the protocol design process, all possible statistical variations and research outcomes need to be discussed and planned. It is critical that all downstream teams are involved in this early scenario development. Teams to be involved include clinicians, statisticians, project management, data management, drug supply management, and regulatory/quality assurance. All these teams need to have input on the developed scenarios and the impact on their disciplines. Without their early involvement, there is the chance that quality and logistical issues will arise that could lead to abandoning the adaptive trial.

Flexibility to accommodate midstudy changes. People, supplies, systems, and quality must be designed and built so that all components can quickly adapt to SSMP analysis and change. Early decisions must be enacted quickly for maximum benefit.

Teamwork is Redefined for Adaptive Trials



Source: Almac

Figure 2. Team participation and communication flow in the phase of adaptive trial design.

The inability to efficiently adapt to study changes has delayed and reduced the effectiveness of many adaptive trials.

Periodic study analysis must have access to clean data. The data points and delivery must be constructed early on so that prompt review of current data can be made. In the case of response adaptive dose-ranging studies that are fully sequen-

The ability to forecast and simulate gives confidence to the success of the adaptive design.

tial, “periodically” really means instantaneously; the randomization scheme must be supported by technology (IVRS or Web-based) that accesses previous randomizations and efficacy and/or safety data virtually while the site is on the phone.

Once decisions have been made, implementation must be done rapidly and with integrity. This often requires changes to be invisible to sponsors, patients, and investigators and the technology and team communication to be quick, complete, and seamless.

Simulation techniques

To facilitate the success of adaptive trials, one suggestion is to use scenario analysis with patient and drug management simulation. The key aspects for any scenario development are patient activity and drug supply needs for that activity. A scenario will encompass these areas with simulation and forecasting data. To clarify, known behavior as dictated by the protocol would be considered a simulation (e.g., visit schedules, dispensing regimes, randomization parameters, dosing decisions, titration events); forecasts are those values, activities or behavioral patterns that are predicted based on previous data, prior experiences or calculated assumptions (e.g., new patient enrollment, drop out rates, titration percentages).

Beyond known protocol information (randomization lists, treatment arms, total patients), forecasting requires patient activity questions and answers for full scenario development.

New patient enrollment forecast. This is a forecast of unknown patient behavior. This data needs to be provided by day, week or month for the length of enrollment. This is a key factor in being able to extrapolate scenario results. This data should be widely understood and agreed upon.

Patient behavior forecasts. These are predicted behaviors critical to either the adaptive decision rules or drug supply. These can include drop out rates, quantity of patients for each dosing decision, percent of patients for titration activity, and any other activity that may impact drug supply management.

Simulations then respond to those forecasts with the prescribed protocol activity. These simulations will focus around treatment arm assignment and visit schedules as well as drug supply extrapolation from all forecasts and patient simulations. The following key simulations must be developed.

Visit schedule simulation. Once the new patient enrollment is forecasted, the resultant visit schedule needs to be extrapolated. This can range from a very simple visit schedule with unchanging visit window and drug dispensing to a complex visit schedule where there are large visit windows, complex dosing decisions based on lab values, and adaptive or prescribed treatment decisions based on titration rules.

Patient required clinical materials simulation. With the

Four Rules To Adapt By

There are four major decision-making rules that drive adaptive modifications. Adaptive trials can involve any one of these four rules, or a combination of them:²

Allocation rule: how subjects will be allocated to the available arms

Sampling rule: how many subjects will be sampled in subsequent stages

Stopping rule: when to drop an arm or stop the trial (for efficacy, harm or futility)

Decision rule: the final decision and interim decisions pertaining to design changes not covered in the previous three rules. Examples of the modifications that can result from these decision-making rules include modifying the sample size, dropping a treatment arm, stopping a study early for success or failure, combining phases, and/or adaptive randomization.

visit schedule extrapolated, the dispensed kits can be estimated based on protocol and forecasted or simulated values. These quantities can be summed or time-phased depending on drug supply strategies, risks, and availability.

Supply chain required clinical materials simulation. This area focuses on both production planning and safety stock decisions. With the supply chain determined (world depots, country depots, sites) and the patient required clinical materials simulation done, a determination can be made on the amount of safety stock held at each supply point. Safety stock decisions include risk aversion factor; drug stability, expiration, and availability; supply point challenges; and confidence in all phased forecasts. Once the full drug demand is simulated (patient required and safety stock), then production decisions can be made based on the time-phased fore-

casts and simulations.

All of these forecasts and simulations work in concert for a variety of scenario developments and analyses, allowing for managers of the various disciplines to review best, worst, and what if scenarios. The ability to forecast and simulate gives greater confidence to the success of the adaptive design and, in many cases, will sort out problems before they happen. Simulations show different implications of patient recruitment, patient randomization schemes, drug supply, product economic impact, clinical outcomes, and sample size.

What success looks like

The culmination of a successful adaptive trial requires significant coordination of people, information, and technology. Implementation of traditional clinical trials allow for more waterfall and stepwise manners; an adaptive trial requires involvement from all disciplines, all the time.

References

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