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Adapting to Adaptive DRUG Development

The promise of cost-savings associated with adaptive clinical trials is an attractive one.

Many drug companies have already put in place trials that use some type of adaptive designs. But most times, companies implement adaptive trial design experimentally, mitigating risk by applying it only during early-phase trials, according to Cutting Edge Information.

An adaptive clinical study is one that includes a prospectively planned opportunity to modify one or more specified aspects of the study design and hypothesis based on an analysis of data, usually at the interim period, according to the FDA's draft guidance for adaptive clinical trials.

Industry experts stress that in an adaptive design, trials changes are planned based on predefined reviews of data. Adaptive clinical trials allow trial administrators to use data collected early in a trial to make changes to the study. Before the trial even begins, trial managers plan when the opportunities for modifications will occur. Modifications could include changes to eligibility criteria, study endpoints, or treatment arms, among others.

"Trial managers could even choose to stop the study altogether if analysis of interim data indicates negative results," says Nicole May, research analyst at Cutting Edge Information. "Adaptive design gives sponsors this go/no-go advantage, something not possible with traditional trial design."

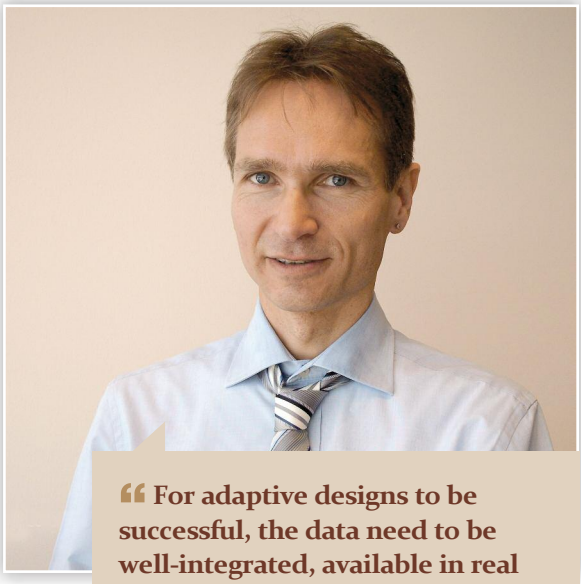
Ms. May says adaptive trials are most likely to be used in exploratory and Phase II studies, as opposed to more complex Phase III trials.

"The risk is greater in Phase III because so many resources have already been invested in the trial," she says. "The FDA has expressed concern about certain adaptive design elements, so companies are hesitant to implement this study design at the pivotal Phase III stage."

Cutting Edge Information conducted a survey of pharmaceutical clinical development executives in 2011. The survey found 100% of survey respondents feel that adaptive design is more effective or substantially more effective than traditional designs. But only 28% of companies employed adaptive clinical trial design at any phase of development.

The interest in adaptive design trials is definitely there, but with the risk to approval and the general uncertainty of the trial stages, companies are still reluctant to stray too far from the established trial procedure, Ms. May says.

"The appeal of lowering drug development costs is driving the interest in an updated trial design, and as so many drugs are hitting their patent cliffs, companies are eager to fill and ad-



> "For adaptive designs to be successful, the data need to be well-integrated, available in real time, and protected by appropriate firewalls."
>
> **JÜRGEN HUMMEL** / PPD

Primary Obstacles to Using Adaptive Designs

- **Statistical challenges:** Limitations to statistical analysis software, along with concerns about the validity of findings obtained through trials employing adaptive design have traditionally slowed the practical application of the method. In recent years, improved statistical software and operational procedures have begun to help legitimize adaptive design.
- **Operational challenges:** To fully harness the adaptations available through adaptive trial design, trial data must be unblinded to at least one party. This controversial step poses the threat of introducing operational bias to the study and runs counter to the long-held practice of the double-blinded, placebo-controlled trial.
- **Acceptance:** Key stakeholders, both internal and external, have been slow to view adaptive clinical trial design as a legitimate alternative to traditional methodologies.

Source: Cutting Edge Information

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>
> **NICOLE MAY** / Cutting Edge Information

vance their drug pipelines as quickly and cost-effectively as possible," she says.

In fact, the Tufts Center for the Study of Drug Development estimates that early study terminations due to futility and sample size re-estimation applied across the portfolio could save sponsor organizations between $100 million and $200 million annually in aggregate costs (direct and indirect costs).

Adaptive trial designs may also save substantial financial resources by helping to reduce the number of protocol amendments. According to Tufts CSDD research, the implementation of each amendment costs organizations nearly half-a-million dollars in direct costs and requires 60 days to implement.

According to Mingxiu Hu, Ph.D., senior director, biostatistics, at Takeda Cambridge US, in an adaptive trial, interim analyses are conducted and changes may be made to the study design if interim results indicate that the original design or the design assumptions are not optimal anymore.

"The adaptation rules have to be pre-specified to prevent the introduction of operational and statistical bias," he says.

Parvin Fardipour, Ph.D., VP of adaptive clinical trials, at Aptiv Solutions, says adaptive designs allow for a more seamless development process.

"One benefit of this approach is efficiency," she says. "For example, efficiency can be increased by combining the objectives of what would traditionally be two separate trials. The benefit of this approach is to cut the overall development timeline."

The benefits of adaptive designs have more companies looking at this model as a way to improve their development processes.

"An increasing percentage of our clients are using adaptive designs to some extent," says Jürgen Hummel, associate statistical science director, at PPD. "The industry has been looking at how to make drug development more effective. There are two ways of doing this: the first is to bring successful drugs to market faster; the second is to identify unsuccessful drugs earlier to release the resources for use on other drug candidates. An adaptive design can assist with both of these goals."

Dr. Hu says another driver for the increase in adaptive trials has been the benefits demonstrated in a series of pilot trials conducted by academic and corporate sponsors alike, which convinced many decision makers about the value of these designs, including increased probability of trial success, shortened development timeline, and reduced study size.

"They may also increase trial efficiency via more focused development in subpopulations, for example biomarker enrichment trials," Ms. May says. "All of these benefits can help bring more effective medicines to the right patient population quicker, as well as reduce the probability of exposing patients to less effective treatments during trials."

Industry experts say, however, adaptive design is not a replacement for other industry programs. Rather, it is complementary and can dramatically change the product development paradigm.

Regulatory Considerations

Dr. Hu says one reason the use of adaptive designs has grown is that, as the methodology matures, regulatory agencies have become more and more comfortable with the designs, in some instances even encouraging their use.

The FDA recommends performing trial simulations before the study to help trial managers plan for many different scenarios. If adaptations depend on multiple factors, these simulations can help trial managers predict and prepare for all possible outcomes. Industry experts say electronic data capture is especially important to these studies since trial decisions are based on collected data. Trial administrators can get data in quickly and accurately with EDC, especially in multinational trials, which leads to faster decisions about trial modifications.

Regulators are encouraging, yet cautious about adaptive trial design, Ms. May says.

"So little research has been done on these trials and companies have such little experience with them that regulators are especially careful when it comes to drug approval," she says. "The FDA outlined in its Adaptive Design Clinical Trials for Drugs and Biologics draft in 2010 recommendations for study sponsors, highlighting low- and high-risk adaptive design elements. Hopefully these guidelines will encourage companies to apply these elements and eventually make adaptive trials more of a widespread practice."

Dr. Hu points out that not all adaptive designs are equally acceptable to regulators.

"Regulatory agencies generally encourage adaptive designs in exploratory trials but will enforce statistical rigor in pivotal trials in terms of type I error control and bias prevention," he says. "For example, some regulators have expressed concerns about Phase II/III seamless designs when dose selection is part of the trial; whereas biomarker enrichment trials seem to be reviewed more favorably. Stopping for efficacy or futility is well-established and accepted. Sample size adaptation is generally acceptable as long as the statistical methodology is sound. An important point in any of these design considerations is to engage regulatory agencies early to gauge their acceptance."

Challenges of Adaptive Designs

Dr. Fardipour says adaptive trials can be complex to implement from a logistics standpoint and require partners who understand the link between design and execution.

"For example, should an interim decision require stopping further recruitment on a dose, there are execution implications," she says. "Those implications include implementing changes to the randomization, coordinating drug supply distribution and ensuring appropriate firewalls are in place to eliminate the possibility of operational bias. Details of interim decisions must be restricted so as to not

introduce operational behavior that could bias the trial."

Industry experts say adaptive trial designs require more up-front planning as well as managing logistical issues. For example, if a design allows for trial discontinuation or the addition of doses, that has challenges for drug supply. Changes to trial supplies have to be made in relatively short notice.

"When making decisions on data that are collected in the study, those data need to be up to date and as clean as possible for that decision-making process," Mr. Hummel says.

He says data need to be integrated and available in real time and protected by appropriate firewalls so that only those people who need to see the information have access to prevent compromising the scientific integrity.

Ms. May says a challenge with adaptive trial design is getting the go-ahead in the first place.

"Winning acceptance by upper management is difficult because, while these trials offer more flexibility and potential savings, they are also riskier when it comes to gaining FDA approval for the drug," she says. "Management is also used to strictly budgeted trials, so when trial managers propose a wide cost range depending on the adaptations, management is reluctant to stray from the traditional trial design."

Ms. May points out that using an adaptive design strategy requires much more collaboration and communication among trial sites, which can be especially difficult for large trials operating worldwide. Communication between trial teams and management is also crucial.

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>
> **DR. MINGXIU HU**
> Takeda Cambridge US

Statistical bias is also a risk of adaptive trial design; the risk of type I errors or false findings in terms of drug efficacy is greater. Changing the trial size based on interim data can also change statistical findings, so the FDA may be hesitant to approve the drug. Operational bias may result from unblinding the data, so bringing in a third-party data monitoring committee to manage the process is recommended.

Dr. Hu says the main challenges in adaptive designs include how to control overall type I errors, i.e., the probability of concluding an ineffective drug is efficacious and how to prevent both operational and statistical bias.

"Adaptive trials also increase operational burden compared with fixed designs and may require additional time during the design stage to reach agreements with regulatory agencies," he says. "Therefore, it's important to engage regulators early to allow sufficient time for a dialogue to avoid potential timeline delay."

Best Practices

Mr. Hummel says a key to adaptive trial success is keeping the designs simple.

"Certain types of adaptive designs can be implemented relatively easily with little additional complexity," he says. "Innovative, more complex approaches can really help speed development. If a compound is being considered for different indications, say in Phase II, an innovative approach would be to perform one study and borrow information across those indications to make a more streamlined decision rather than running separate studies for separate indications and then analyzing them individually."

Ms. May says the main keys essential to a successful adaptive clinical trial are spotless record keeping and data management, as well as internal and external communications.

"Trial data are especially important when the drug is up for approval, as bias is much more likely to occur in an adaptive trial design," she says. "Constant collaboration throughout the study will help reduce this bias. Meeting with the FDA before and throughout the trial will ensure trial administrators conduct the study in a way that leads to a successful drug approval. This is only possible through communication among all levels of the trial. The adaptive elements of the trial may necessitate changes in treatment arms and dosages or changes in drug supplies, and communication with third-party data monitors will be imperative."

Dr. Hu says for each basic type of adaptive design, the necessary technology and statistical methodology are already in place.

"For some complex designs, further statistical research may be needed to ensure the appropriate control of the overall type I error rate," he says. "Commercial software has been developed for monitoring adaptive designs to minimize operational and statistical bias."

Dr. Hu says one key consideration is to prevent or minimize operational bias or the perception of it. In an adaptive trial, an independent design statistician, who has no operational involvement in the study, is recommended to set up the adaptation rules before the study starts. He also recommends that an appropriate firewall be set up to prevent the study team's access to the adaptation rules and interim results. PV

Adaptive Design Trends

- **Adaptive design** has a critical role to play in modern protocol planning and needs to be even more widely adopted across industry. Central to this concept is scenario planning through trial simulation, which acts as a critical stress test for protocol design and a key tool to demonstrate value of adaptive design to multiple stakeholders.
- **Simple adaptive designs** should be considered part of good clinical practice and routinely applied in both exploratory and late-phase trials as an insurance policy to either stop early for futility or re-assess the sample size to save the trial. Evidence from leading companies shows that futility stopping saves upward of $100 million per annum when applied at the portfolio level.
- **Different types of adaptive design** must be deployed in exploratory phase trials where key decisions on dose, endpoint, and patient population have to be made before pivotal trials can start. Futility stopping in Phase III indicates product failure of which one of the root causes is poor dose selection at Phase II.
- **Phase II adaptive dose-finding trials** must be implemented widely to ensure that late-phase attrition is addressed robustly across the industry. Both the FDA and EMA are urging pharmaceutical companies to use these techniques more widely and are ready to provide support.
- **Newer trial designs** will require re-appraisal of the technology and operational processes used to deliver such trials. Integrated technologies are now readily available, but their adoption will need the support of pharmaceutical executives to drive the necessary change within their companies to ensure success.

Source: Tufts Center for the Study of Drug Development