



What are Adaptive Design Clinical Trials?

Adaptive clinical trial designs have been used extensively in medical device development and the lessons learned from those studies are now being applied to drug development. Adaptive designs can potentially reduce the number of patients in a trial and the number of trials overall. Trials with an adaptive design may even provide more informative trial results. The added flexibility that adaptive design offers may also increase acceptability to stakeholders.

Adaptive design is particularly useful for adequately controlled clinical safety and efficacy trials. They can also be quite beneficial in early-phase studies and exploratory trials, as well as later trials conducted to satisfy post-marketing commitments. Using adaptive design in an exploratory setting can allow evaluation of a broad range of doses, regimens, populations, and so forth, with the opportunity to discontinue evaluation of suboptimal choices. Besides additional flexibility, this approach has an ethical benefit of exposing fewer subjects to suboptimal treatments.

Adaptive vs. Non-Adaptive Clinical Trial Design

To understand what adaptive design is and how can it be used effectively, the FDA released its final guidance on [“Adaptive Designs for Clinical Trials of Drugs and Biologics”](#) in November 2019.

The guidance defines an adaptive design as “a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in that trial.”

A familiar example of adaptive design exists in early-phase dose escalation studies. These studies often employ prospectively planned interim reviews of [pharmacokinetic \(PK\)](#) and safety data by a review committee, which then makes decisions about how to proceed. In such cases, the protocol should clearly and prospectively define committee membership and criteria for whether to stop dosing, repeat the previous dose, or proceed to a higher dose. Non-adaptive trial designs do not include such opportunities for modification.

NON-ADAPTIVE CLINICAL TRIAL DESIGN

In a non-adaptive study design, [critical study parameters are planned](#) using assumptions and best estimates. This includes things like population means and event rates, variance, dose-response effect size and location, and discontinuation rates. This can work well when estimates and assumptions are accurate, but problems can arise if they are not.

[Non-adaptive study designs](#) often include elements to reduce risks associated with uncertainty. For example, if the study is meant to determine dose-response, the protocol may include multiple fixed-size randomized groups to ensure that an optimal dose is captured. Such design decisions are made with the understanding that several groups will likely be treated with suboptimal doses. In this method, the study design trades efficiency in exchange for reducing the risk that the optimal dose will be missed. In contrast, with an adaptive design, you may not have to compromise efficiency to ensure that the optimal dose is captured.

ADAPTIVE CLINICAL TRIAL DESIGN

The central advantage of adaptive design is the ability to include prospectively planned opportunities for modifying study design elements and hypotheses based upon interim data analyses. Such modifications must be prospectively planned in the protocol and any interim analyses need to control for statistical bias.

An example of adaptive design could be using a model-based approach to select Phase 2 doses. The model could then be adapted as interim data becomes available and used to inform modifications to the study design in order to reduce the number of subjects receiving suboptimal doses. This allows a greater focus on doses that have the potential for efficacy. Adaptive design can also include futility criteria, which are useful in cases where the drug may not have efficacy. Rather than waiting for study completion, an adaptive design can use interim data to evaluate whether enrolling more subjects would lead to a failed study.

Another example of where adaptive design might be beneficial is in determining an appropriate sample size for the study. In a conventional trial, there is a risk of underpowering a study if estimates of variance and treatment effect are overly optimistic; likewise, if these parameter estimates are too conservative, then you can end up with an excessively large study population. If a study is underpowered, then the study data will not be sufficiently robust from a statistical standpoint to support meaningful conclusions. If the study population is too large, then significant amounts of time and money are wasted. Using an adaptive design, sample size can be adjusted based upon accumulating study data in a way that avoids these undesirable outcomes.

What Can Be Modified in Adaptive Trials?

While modifications are common in adaptive design trials, not all may be appropriate for every trial. You should carefully consider which aspects to make “adaptive,” as inappropriate choices or too much flexibility may introduce bias. Examples of prospectively planned modifications that may be included in an adaptive design trial include:

- Adaptations to randomization procedures, which can lead to more subjects being assigned to more promising treatment arms
- Abandoning or adding treatment arms or doses
- Adaptations to the sample size based on interim results
- Adaptive enrichment to the patient population
- Pre-specified stopping rules for efficacy or futility

Four Key Considerations for Adaptive Designs

The 2019 guidance identifies four key principles to consider when designing an adaptive design trial:

1. Controlling the chance of erroneous conclusions
2. Estimating treatment effects
3. Trial planning
4. Maintaining trial conduct and integrity

CONTROLLING THE CHANCE OF ERRONEOUS CONCLUSIONS

One strategy used in adaptive design is to plan a preliminary, unblinded test halfway through the planned trial to determine if an efficacy endpoint has been met. Achieving an endpoint early can significantly reduce the time and resources required for the trial. If the endpoint has not been met, then the trial continues with a subsequent test when the trial is completed. In the second case, the increase in the number of tests will increase the error probability of this final analysis. Therefore, potential impacts to the statistical validity of the final analysis should be considered during prospective planning.

Non-adaptive trials have historically relied on statistical theory to ensure that Type I and II error are properly controlled. This commonly involves using a pre-specified significance level, such as 5%. However, this approach is not feasible for designs that adapt several elements.

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In such cases, [clinical trial simulations](#) may be a useful tool to aid in adaptive trial design. Hypothetical clinical trials may be simulated under a series of assumptions to produce an estimate of error under those assumptions.

ESTIMATING TREATMENT EFFECTS

One potential source of bias could be changes involving the type of data in the primary analysis (e.g., endpoints, populations), which may make interpretations of treatment effect difficult. Methods for adjusting estimates to reduce bias, if available, should be prospectively planned and used for reporting results. In cases where such methods may not always be available, at a minimum the extent of bias should be evaluated, and treatment effect estimates should be presented and interpreted with appropriate caution.

TRIAL PLANNING

Prospective planning should be rigorous and include the anticipated number and timing of interim analyses, the type of adaptation(s), the statistical inferential methods to be used, and the specific algorithm governing the adaptation decision. A comprehensive analysis plan developed prior to initiating the trial increases confidence that adaptive decisions were not made based on accumulating knowledge in an unplanned way.

MAINTAINING TRIAL CONDUCT AND INTEGRITY

Knowledge of accumulating data in a trial may affect the course and conduct of a trial, as well as the behavior of its sponsor. Thus, it is strongly recommended that access to comparative interim results be limited to individuals who are independent of those conducting or managing the trial. When planning for an adaptive trial, it is important that possible sources and consequences of trial conduct issues are identified. Plans should be in place to avoid these issues, including processes intended to control blinding and to document access throughout the trial, since these and similar issues are often impossible to adjust after the data have been collected.

Potential Challenges of Adaptive Design

In addition to the considerations outlined above, there are some potential limitations that should be considered when choosing an adaptive design. While the number of trials may be reduced using an adaptive design, critical insights may be missed during a rapid interim analysis that might

have been captured by more thoughtful analyses following an exploratory study. This may result in inadequate recognition of safety issues or other critical information related to treatment response, interactions with concomitant therapies, or other variables. Such oversights can be costly and may extend overall development timelines.

Finally, adaptive design may not be the best option for all clinical trials. This includes short studies (e.g., 2-8 weeks) in populations that can be recruited very quickly (i.e., less than 3-6 months), since recruitment needs to be halted while interim analyses are conducted. Conversely, an adaptive design may be well suited for a longer study where interim data from a short-term endpoint (e.g., at 6 weeks) is used to predict a long-term endpoint (e.g., 6-12 month), since halting patient recruitment is unnecessary in this case.

Adaptive designs tend to work best and with less risk when only a few issues (e.g., dose, population subsets, and endpoints) need to be examined. For programs where there is significant uncertainty around many parameters, running an exploratory trial prior to designing the “adequately controlled” trial may provide additional insights regarding at least some of these parameters. This can reduce uncertainty and make the approach more efficient and informative.

Conclusions

Adaptive design clinical trials may offer key advantages over conventionally designed trials, including the flexibility to make prospectively planned modifications to certain elements of the study design and achieve more informative and efficient study outcomes. However, using adaptive design is not without risks. It is therefore imperative that all study design decisions are carefully considered and prospectively specified.

Are you considering designing an adaptive design trial? [Contact one of our senior scientists](#) to ensure you get the most out of your study design.

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