Adaptive Designs for Medical Device Clinical Studies

Introduction

Traditionally, clinical trials are first designed, then conducted as prescribed by the design, and once the data are ready, analyzed according to the prespecified analysis plan. Although this practice is straightforward, traditional designs are not without limitations, particularly in the context of rapidly evolving medical device technologies. The rigidity of fixed study designs may hinder potential adaptability to emerging study data trends, leading to various inefficiencies in time and resources.

Adaptive designs have gained recent attention due to their potential to optimize efficiency, flexibility, and cost-effectiveness in the clinical trial process through dynamic modifications based on interim data analyses at predefined interim points. By allowing for real-time adjustments to trial parameters, adaptive designs have the potential to address the shortcomings of traditional fixed study designs while enhancing patient safety, optimizing resource allocation, and accelerating regulatory approval. This white paper aims to provide an overview of adaptive designs, highlight their benefits and potential limitations, and introduce concepts of sample size re-estimation (SSR) and group sequential designs. We focus below on clinical studies regulated by FDA, but the same methods can be used for studies being regulated by other notified bodies or for studies not intended for regulatory approval.

What Are Adaptive Designs?

When properly implemented, adaptive designs can improve study efficiency by decreasing the amount of time to study completion, reduce study costs, and/or increase the chance of study success. Two underlying principles, controlling the chance of erroneous conclusions, and minimizing operational bias, are crucial in ensuring a clinical study with valid scientific evidence.

Adaptive Design
[*uh*-**dap**-tiv dih-**zahyn**]
noun

A clinical study design that allows for prospectively planned modifications based on accumulating study data without undermining the study's integrity and validity.[1]

It is important to note that in most cases, modifications must be planned in advance and communicated in the clinical trial protocol prior to study initiation to preserve the integrity and validity of the study. Sponsors are encouraged to consult with the FDA prior to embarking on an adaptive design to avoid possible issues such as protocol resubmission, IRB-related delays that can hinder the study timeline, and IRB-mandated reconsenting.

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In specific circumstances, design modifications after the study begins can be scientifically valid if the modifications are made without knowledge of the outcome results by treatment. In this case, the FDA will expect sponsors to justify the scientific rationale as to why the approach is appropriate and preferable and demonstrate that unblinded outcome data have not been accessed, and that the data access is safeguarded. All analyses should still be prespecified in the protocol or statistical analysis plan amendment prior to conducting the analyses.

When Are Adaptive Designs Feasible?

Generally, adaptive designs are feasible when the time to ascertainment of the primary outcome is short relative to a longer enrollment period, as this ensures adequate time to implement changes in the study design. Adaptive designs are also feasible when studies are designed with a small number of primary endpoints, as proper statistical control of the type I (false positive) error may be difficult to determine when there are a larger number of primary endpoints under the adaptive design.

What Are the Benefits of Adaptive Design?

Adaptive designs offer a multitude of benefits when compared to a traditional fixed design. A key advantage lies in their ability to enhance trial efficiency by enabling

real-time modifications to study parameters based on accumulating data, which optimizes trial efficiency by improving resource allocation and trial duration. This can save time, money, and resources in clinical trials, as studies with interim analyses can stop early for effectiveness and/or futility. A trial with two or more investigational arms could also plan to drop one arm based on accumulating data. Doing this could ultimately expedite the translation of innovative medical technologies from concept to market, allowing for a timelier development of medical devices.

Moreover, adaptive designs may increase the chance of study success. Based on accumulating data, planned SSR could lead to an adjustment in a study's sample size, converting an underpowered study that was likely to fail into a study that is more likely to succeed. Doing this allows for adjustments in trials when there is a significant treatment effect but smaller than originally estimated.

Additionally, from an ethical standpoint, adaptive designs can enhance patient safety and optimize the treatment of enrolled subjects by allowing for early detection of treatment effects and timely adjustment to trial interventions. This allows for proper safeguarding of patient welfare from ineffective or unsafe treatments at the earliest stage, as well as increase the probability that a patient is assigned to a treatment that would be more likely to provide a better treatment outcome.

What Are the Challenges of Adaptive Design?

While adaptive designs offer significant benefits, they also present several possible challenges that must be carefully addressed. Preplanned study design modifications may require more effort during the design stage. Adaptive designs necessitate the anticipation of various potential adaptations and their associated statistical and operational implications at the trial design process. As a result, the design stage of adaptive design clinical trials may require more time, resources, and collaboration among multidisciplinary teams to ensure that the trial is appropriately designed to achieve its objectives while minimizing risks and maximizing potential treatment benefits. It is important to note that adaptive designs that are overly complicated can also lead to difficult planning and provide results that are difficult to interpret. Additionally, the maximum sample size may be greater and study duration may be longer than the traditional nonadaptive design.

Adaptive Design Using Unblinded Data

Group sequential designs and sample size adaptation are the most widely used adaptive designs based on unblinded data.

Adaptive designs may increase the chance of study success

SSR

SSR allows sponsors to adjust study sample size based on prespecified interim analyses while the trial is ongoing to avoid underpowered studies and control the type I error in hypothesis testing, thereby enhancing the power and precision of the trial. Initial sample size calculations are usually based on estimates of variance or effect size with, in some situations, substantial uncertainty. An adaptive design using SSR allows sponsors to potentially adjust the sample size based on unblinded interim results from the clinical trial. One or more SSRs can be planned, but it is important to note that SSRs must be preplanned to mitigate biases and maintain trial integrity.

A commonly used SSR approach that is widely accepted by regulators is the Mehta-Pocock Promising Zone approach. Under this approach, the SSR is based on the evaluation of the conditional power. Conditional power is the probability of achieving statistical significance at the completion of the study, given the interim data observed. If the conditional power is within the promising zone, then sample size is increased by just the right amount to recover the targeted level of power (e.g., typically, 80% or 90%). If the conditional power is below the promising zone, then the sample size will remain the same since the interim result is so disappointing that it is not worth increasing the sample size. If the conditional power is above the promising zone, then the sample size will also remain the same since the interim result is sufficiently favorable that the trial continues to the original sample size. Type I error is not compromised when increasing the sample size using this promising zone approach.

Group Sequential Designs (GSDs)

GSDs allow for interim unblinded analyses of the primary endpoint with the possibility of stopping a study early for overwhelming efficacy (success) or futility. GSDs require

a prespecified statistical plan that accounts for the predetermined interim analyses and appropriate adjustments to the significance level (alpha). GSDs offer several advantages, including increased statistical power, reduced trial duration, and enhanced flexibility in response to evolving clinical evidence. If a medical device performs better than expected and there are sufficient safety data, GSDs can enable early stopping for success, saving time and resources. The FDA recommends utilizing a data monitoring committee (DMC) to examine the data in a protected and confidential manner to implement the GSD.

Alpha spending functions play a pivotal role in GSDs by guiding the allocation of alpha (type I error) across interim analyses while maintaining the overall significance of the trial, as multiple testing for efficacy can inflate type I error. Common types of alpha spending functions include the Pocock approach, which derives constant critical values across all interim analyses to maintain the overall significance level, and the O'Brien-Fleming approach, which allows higher significance levels at later interim analyses (more alpha can be "spent" at later analyses).

Other Types of Adaptive Design

Other types of adaptive designs offer innovative approaches to optimize efficiency and flexibility in medical device clinical trials. The drop-the-loser design allows for the early elimination of an experimental treatment arm during the study that demonstrates inferior efficacy or safety, which can save valuable time and resources. Seamless designs may include a feasibility investigation that smoothly transitions from early-phase device development and evaluation plans to a pivotal study in a preplanned manner, pending no significant changes to the device or study. For example, the feasibility portion of a seamless study design could incorporate several device configurations, where only the configuration that showed the most promising results in the feasibility stage would seamlessly transition into the pivotal study. In some cases, all data in a seamless design may be included in the final analyses. Additionally, adaptive enrichment plans to investigate prespecified patient subgroups that may have different responses to the experimental device at one or more interim looks using unblinded data. This methodology allows for the preplanned modification of patient eligibility criteria or study populations based on interim data analysis, thereby targeting specific subgroups more likely to benefit from the experimental device.

How Can Avania's Expertise Help With Adaptive Design?

Avania has extensive expertise and experience with supporting its clients in all stages of the study when considering and implementing adaptive designs. Some of the support we provide, which is tailored to the client and nature of their study, include the following:

- Assessing whether adaptive design is feasible for the study and more advantageous compared to the nonadaptive conventional design
- Identifying which adaptive designs are appropriate for the study and what are the benefits and limitations of each design
- Implementing adaptive design in the protocol and the statistical analysis plan, taking into account the regulatory authorities' requirements for a successful submission
- Conducting the analysis with accuracy while preserving blinding and minimizing operational biases

Reference

[1]Adaptive Designs for Medical Device Clinical Studies, Guidance for Industry and Food and Drug Administration Staff. U.S. Department of Health and Human Services Food and Drug Administration. Published 2016 July 27.