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Clinical Trials, Meet Adaptive Design

Adaptive design (AD) clinical trials have become increasingly popular as they offer the ability to reduce the overall time and cost of running clinical trials. They improve patient safety by minimizing exposure to unsafe or non-efficacious treatments. With its 2019 final guidance on Adaptive Design Clinical Trials for Drugs and Biologics, the U.S. Food & Drug Administration's (FDA's) position on adaptive designs for clinical trials is favorable. The FDA encourages companies to consider utilizing adaptive designs to expedite and improve efficiencies for identifying the clinical benefit of new therapies. The European Medicines Agency (EMA) has also shown support for the adaptive pathways.

Veristat is a pioneering leader in planning and executing adaptive design studies – delivering the expertise to determine the appropriate applications for adaptive designs, selecting and simulating the right design, and providing the operational expertise to execute the design with successful outcomes. Overall, Veristat's goal is to help expedite decision-making for more efficient clinical trials.

Adaptive Design Trial Defined

An adaptive design clinical study is defined 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 the trial (FDA 2019 Final Guidance)[1].

Benefits of and Considerations for Adaptive Designs in Clinical Trials

While adaptive designs can be advantageous in certain circumstances, they are not well-suited for every clinical trial. Before embarking on an adaptive design approach, it's necessary for sponsors to understand the possible benefits, the limitations, and when to apply adaptive designs.

AD Benefits
› Reduces cost, time & required resources
› Increases the chance of a successful study via midcourse corrections
› Reduces time to market
› Mitigates risks in pursuing ineffective strategies
› Improves patient safety
› Facilitates better evidence-based decision-making

AD Considerations
› Requires more intensive planning
› Requires more frequent interaction with regulatory agencies
› Improper execution can introduce bias
› Confounding can result from adaptations
› May require larger sample sizes
› Statistical significance (alpha) penalties apply

When to Consider Adaptive Designs

According to the FDA[2], adaptive designs are highly encouraged for clinical trials in the following applications:

Oncology trials – Particularly in early phase dose-finding trial designs that use intermediate or accelerated approval endpoints for decision-making

Rare disease trials – Limited patient populations can use supplemental data from earlier run trials, disease progression analytical models or previous adult trials

Trials with large cardiovascular risk – Used for safety monitoring to leverage control patient from other sources

Veristat has proven expertise in designing and running adaptive design approaches for clients within rare disease and oncology therapeutic areas – two areas where trial design is more complex, patient recruitment represents unique challenges, and the application of precision medicine approaches is increasing.

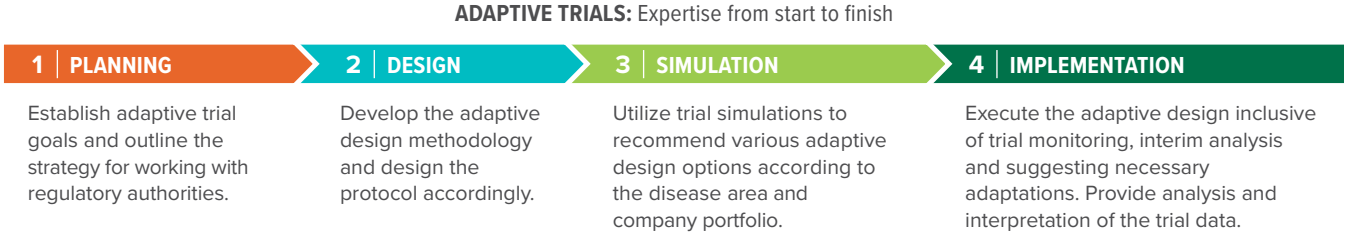
Proven Expertise for Adaptive Trial Design, Simulation and Execution to Accelerate Clinical Development Success

If you are planning a clinical trial, you should consider an adaptive design approach. Veristat's experts will help you navigate the entire process, from determining whether your product is a good candidate for an adaptive design, through to the operational execution of the adaptive design trial. Additionally, Veristat's experts have led the operational execution of many adaptive trials, including AD trials for cancer vaccines and bacterial infections.

End-to-End Solutions to Optimize Trial Outcomes

Veristat's teams can develop both simple or complex adaptive designs and corresponding statistical analysis plans (SAPs) based on your development program goals. We collaborate with regulators, biostatisticians, clinical and medical affairs teams, and any other aligned colleagues to ensure design goals and operational execution best practices are well understood from the start to create successful regulatory approval outcomes. Our end-to-end adaptive design approach provides a programmatic approach to ensure success (Figure 1).

Figure 1: Adaptive Trial Design Services



Adaptive design trials require significantly more upfront pre-planning than a conventional design trial. This planning can lead to longer start-up timelines up front and additional cost at the beginning of the trial. These delays can be offset over the course of a successful adaptive trial by shortening the overall trial timeline. Examples of adaptive trial planning considerations are explained in Figure 2.

Figure 2: Adaptive Design Trial Pre-Planning Considerations

- Selecting & simulating multiple adaptive designs
- Calculating the sample size
- Performing simulations on the adaptive design selected
- Writing statistical analysis plan (SAP)
- Design of clinical trials and product program
- Data analysis planning
- Protocol development
- Design & implementation of randomization systems including adaptive randomization systems
- Data analysis
  - Planned analyses including designing analysis data sets, statistics, and displays
  - Interim analysis for adaptive designs and data and safety monitoring boards (DSMBs)
  - Exploratory analyses for publications, abstracts, and marketing
  - Non-clinical trial data from epidemiologic studies and pre-clinical studies
  - Mechanistic data
- Generation of efficient data display using Tables Listings Figures (TLF) library
- Specialized statistical consultation
- Customized adaptive statistical training

CASE STUDY #1: ONCOLOGY

Operationalizing a Complex Oncology Adaptive Design to Accelerate a Go/No-Go Decision

Situation: A clinical-stage biopharmaceutical company came to Veristat with a complex statistical methodology for running a Phase II oncology adaptive design trial with the goal of expediting a go/no-go decision for a specific patient population. The sponsor's challenge was that they didn't understand the complex adaptive design methodology enough to explain it to their senior management team and investors, nor could they determine how to operationalize the methodology into a trial design.

Solution: Veristat reviewed the complex biomarker-driven (a.k.a. adaptive enrichment) design and methodology and explained it to the sponsor's teams and investors, and to the regulatory agencies, sites, project teams and clinical study vendors that would need to understand and implement the adaptive design. The adaptive enrichment design trial would need to run across sites throughout North America, Europe, and Japan, and therefore our lead Biostatistician flew to Japan to sit with the Japan PMDA to explain and defend the adaptive design approach. After extensive discussions with all regulatory agencies, the FDA, EMA, and PMDA approved the study design to begin within their respective countries.

Impact: At the interim analysis, the original study was stopped for futility as the study drug failed to show a treatment effect for the specific biomarker patient population. The study did achieve its goal of getting to a no-go decision quickly, enabling resource reallocation to other cancer types, indications and studies. With Veristat's help, the product received FDA approval for another cancer indication.

We Deliver Successful Outcomes Through Adaptive Design Trials

"We have identified a biomarker in mesothelioma that may predict increased sensitivity to our product. We felt strongly that the application of an enrichment design would help us to accelerate the program to a potential regulatory decision. We are excited to have Veristat's experience in enrichment trial design and execution supporting this trial."

– Chief Medical Officer, Oncology-Focused Biopharmaceutical Company

Types of Adaptive Designs

Our experts will carefully consider which design(s) best achieve your goals most expeditiously. We routinely consider and simulate the following types of adaptive designs:

Simple Adaptive Designs	Complex Adaptive Designs
› Group-Sequential Design (GSD)	› Adaptive Dose Finding
› Sample Size Re-Estimation (SSR)	› Adaptive Randomization Design
› Adaptive Dose-Escalation Design (ADED)	› Dropping Treatment Arm (or Pick-the-Winner Design)
	› Seamless Phase I/II or II/III Design
	› Population Enrichment Design (a.k.a. adaptive enrichment, biomarker-driven design)

[1] https://www.fda.gov/media/78495/download
[2] https://www.fda.gov/downloads/Drugs/NewsEvents/UCM601630.pdf

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CASE STUDY #2

Pick-the-Winner Design Reduces Patient Sample Size Needed for Rare Disease Study by 30%

Situation: A rare disease company needed to determine whether their combined Phase II/III international study would benefit from an adaptive design.

Solution: Veristat prepared and simulated two trial designs – a pick-the-winner adaptive design and a conventional design approach. By utilizing a pick-the-winner design, the company can reduce the patient sample size by 30% as compared to the conventional design, which enables clinical trial cost and time savings.

Impact: The rare disease company selected to launch the pick-the-winner adaptive trial design.

Consult Our Adaptive Design Experts

To learn more about Veristat or how we can assist you in determining if an adaptive design is right for your program, reach out to us today.

www.veristat.com/adaptive-designs