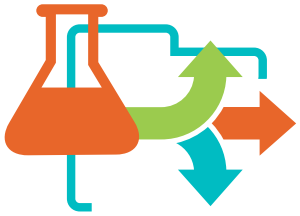
VERISTAT

Clinical Trials, Meet Adaptive Design

Adaptive design (AD) clinical trials are increasingly popular as they offer the ability to reduce the overall time and cost of running clinical trials. And, they improve patient safety by minimizing exposure to unsafe or non-efficacious treatments. With its most recent 2016 Final Guidance on Adaptive Designs, the U.S. Food & Drug Administration's (FDA's) position on adaptive designs for clinical trials has become more favorable. The FDA is now encouraging companies to consider utilizing adaptive designs to expedite and improve efficiencies for identifying the clinical benefit of new therapies.

Veristat is a pioneering leader in adaptive designs – delivering the expertise to determine the appropriate applications for adaptive designs, selecting and simulating the right design, and then providing the operational expertise to execute the design with successful outcomes. Overall, our 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 study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study (FDA 2016 Draft Guidance)[1].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 single clinical trial. Before embarking on an adaptive design approach, it's necessary to understand the possible benefits, the disadvantages, and when to apply adaptive designs.

AD Benefits	AD Considerations
› Reduces cost, time & required resources	› Requires more intensive planning
› Increases the chance of a successful study via midcourse corrections	› Commands more frequent interaction with regulatory agencies
› Reduces time to market	› Improper execution can introduce bias
› Mitigates risks	› Confounding can result from adaptations
› Improves patient safety	› Certain ADs may require larger sample sizes
› Facilitates better decision-making	› 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 are increasing.

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

If you are considering an adaptive design approach, our 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. In the past two years, we've **designed and simulated 18 adaptive trials** for 12 distinct companies. Additionally, our 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

Our teams can develop both simple or complex adaptive designs and corresponding statistical analysis plans (SAPs) based on your development program goals. We collaborate with all stakeholders 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).

Adaptive Design Staff Expertise

100%
of Biostatistics and Programming team trained in both adaptive design and conventional trial designs

>75
have advanced degrees

8
biostatisticians can prepare adaptive designs and simulations

4
senior consultants for adaptive design

Figure 1: Adaptive Trial Design Services

ADAPTIVE TRIALS: Expertise from start to finish

1 PLANNING	2 DESIGN	3 SIMULATION	4 IMPLEMENTATION
Establish adaptive trial goals and outline the strategy for working with regulatory authorities.	Develop the adaptive design methodology and design the protocol accordingly.	Utilize trial simulations to recommend various adaptive design options according to the disease area and company portfolio.	Execute the adaptive design inclusive of trial monitoring, interim analysis and suggesting necessary adaptations. Provide analysis and interpretation of the trial data.

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. However, this 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[3]

- 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 (aka 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 recently received FDA approval for one of the other cancer indications.

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 (aka adaptive enrichment, biomarker-driven design)

[1] https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf
[2] https://www.fda.gov/downloads/Drugs/NewsEvents/UCM601630.pdf
[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3248853

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: Today, the rare disease company is planning 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 to determine if an adaptive design is right for your program, reach out to us today.

www.veristat.com