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# Essential Considerations for Adaptive Design in Clinical Trials

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## Clinical Trials, Meet Adaptive Design

In 2016, the Food and Drug Administration (FDA) released final guidance on adaptive design in medical device trials. The final guidance refined their 2010 draft guidance on general adaptive clinical trial design, with the intent to provide clarity on adaptive design planning and implementation, and to encourage its use. By obtaining a deeper understanding of the FDA's final guidance, as well as the benefits and challenges of adaptive clinical trials, trial designers and sponsors can select the approach that best achieves their statistical, ethical, timing and financial goals.

## In this brief, learn about…

**Benefits and challenges of adaptive design**

**Key threats to adaptive study validity and integrity**

**Practical approaches for successful designs**

# Benefits and Challenges of Adaptive Design (AD)

According to the FDA's final guidance on adaptive designs for clinical trials, there are several key benefits to a flexible and innovative study design approach.

### Advantages of Adaptive Design

- Reduced cost, time and required resources
- Increased chance of a successful study via mid-course corrections
- Reduced time to market
- Risk mitigation
- Increased likelihood of drug delivery to the right people at the right time and in the right amounts
- Improved participant protection via reduced exposure to potentially ineffective or unsafe treatments
- Optimized milestone decision-making for products

Despite the advantages of AD, challenges still exist that may make it inappropriate or infeasible to implement for certain types of studies. Understanding the major considerations for AD can help sponsors identify the studies best suited for this trial design approach.

> *"There is a real danger that an unplanned modification to the study may weaken its scientific validity… Sponsors should anticipate and plan for modifications based on a variety of possible scenarios that could occur."*
>
> **Food and Drug Administration (FDA, 2016)**

### Considerations for AD

- Requires more intensive planning during the design stage, and may require ongoing in-depth interaction with the FDA
- Improper execution results in introduction of bias and difficulty characterizing true effect of the intervention or device
- Confounding can result from adaptations when results pre- and post-change are very different
- Certain ADs may require larger sample sizes or longer study durations if the study is carried out to the final stage
- Statistical significance (alpha) penalties apply whenever adaptations are made, and *p*-values can be challenging to define and compute

Similar to other trial design approaches, AD may also necessitate the involvement of independent data monitoring committees (DMCs) and/or partnering with experienced biostatistical contract research organizations (CROs). Some of the challenges of planning and implementing an adaptive approach may become benefits in their own way. For example:

- Upfront intensive planning can enable more streamlined implementation, more justified selection of study design, and identification of numerous preventable failure scenarios
- Increased interaction with the FDA can boost the early adoption of time- and resource-saving modifications and reduce the chance of setbacks after the study begins

## Protecting Integrity and Validity

Adaptive trial design can only meet appropriate standards for study integrity and validity if it starts with pre-determined options or *prospectively specified* triggers and methods for modification.

Adequate planning for anticipated, allowable adaptations is essential. Without it, studies open themselves to threats to integrity (credibility) and validity (the ability to draw sound inferences). The adaptations must be defined — with clear, specific parameters — in advance. However, specific, planned and scientifically valid methodology is more critical than exact quantifications of the degree of adjustment. For example:

- For an adaptive study to enable sample size re-estimation, it is important to determine in advance the calculation method for re-estimating sample size and the criteria for determining whether the sample size should or should not be increased. It is less crucial to provide the exact sample size increase planned for each possible effect size.

### Considerations for AD Planning

There are many opportunities for adaptations to introduce threats to study integrity and validity. Sponsors and trial designers should understand that three of the following considerations are inherent in all trial design approaches, with an additional two for adaptive designs:

**ALL TRIAL DESIGN APPROACHES**

- Changes in inclusion/exclusion criteria can introduce confounding and make generalizability difficult
- Missing data can lead to bias during statistical analysis
- Combined analysis of sub-groups may mask trends in country or regional efficacy

**ADAPTIVE DESIGN APPROACHES**

- "Pick-the-winner" adaptive designs may result in heterogenous pre- and post-adaptation study groups
- Multiple ADs include subjects from the interim analysis in final data calculations as well, double counting them

By being aware of these possible threats in advance, sponsors can plan strategies for overcoming these weaknesses by building in statistical and methodological safeguards.

## Optimize Approaches for Successful Design

As in conventional clinical study design, advanced preparation and careful consideration of possible threats to validity and integrity pay dividends when an AD trial is designed to avoid those challenges. There are many specific strategies for exploring the optimal trial design, identifying specific threats and minimizing potential pitfalls.

> *"When properly implemented, adaptive design can reduce resource requirements and/or increase the chance of study success."*
>
> **FDA Final Guidance, May 2016**

TABLE 1

**ADAPTIVE DESIGN OPTIONS**

- Group sequential design
- Sample size re-estimation
- Combined group sequential and sample size re-estimation
- Bayesian sample size adaptation
- Dose adjustment treatment arms
- Randomization ratio changes
- Early stopping for superiority and non-inferiority
- Adaptive enrichment design
- Adaptations based on total information
- Device or endpoint adaptations
- Seamless design

- **Explore the gamut of study design options for adaptive clinical trials.** The most popular designs are group sequential and sample size re-estimation, but numerous options exist and could be the most appropriate for certain study needs. The FDA may accept any AD that protects subject safety, trial efficiency, and study validity and integrity. The emphasis from the agency is to ensure that the possible implications of the trial on subject safety, Type I error, and power are well-understood prior to trial inception. (Table 1.)
- **Use clinical trial simulation.** This process models clinical trials using computer programs to determine if AD is feasible and better than conventional options. The process is fast, affordable and can provide critical insight into the pros and cons of selecting an adaptive approach for a given study. Clinical trial simulations can help:
  - Model complicated situations with strong Type I error control
  - Calculate power, sample size requirements, confidence intervals and many other statistical characteristics for different designs
  - Illuminate the validity of different designs under various clinical settings or protocol deviations
  - Predict trial problems and identify possible solutions
  - Visualize study processes and possible results from recruitment through completion under numerous scenarios
  - Identify and justify selection of a particular study design
- **Engage a data monitoring committee (DMC) and/or independent research team.** Independent DMCs and contract research organizations can fulfill several roles for the protection of adaptive clinical trial integrity and validity:
  - Calculation and review of interim data to recommend a course of action while maintaining sponsor blinding
  - Reduction of possible bias by minimizing the number of people informed of interim results
  - Shielding of investigators and study participants from implemented adaptations
  - Maintenance of a separate adaptation procedures document outside of the primary statistical analysis plan
  - Monitoring the protocol during the adaptation process and/or carrying out the adaptations

- **Be proactive about communicating with regulatory and review entities.** This includes early and frequent communication with the FDA to ensure an acceptable AD approach, as well as clear description and documentation of the adaptive study design for institutional review boards (IRBs). FDA submissions for adaptive designs require additional information compared to conventional studies, such as justification for AD selection, plans for ensuring integrity during adaptations, analysis of the impact of adaptation on operating characteristics, and more.

Upfront efforts for appropriate selection of adaptive trial design options can help determine whether AD is truly the best option for a particular study. Ideally, careful design selection also aids in the prospective selection of adaptation methodologies, streamlines study conduct and improves the chances of a successful trial. It also reduces the risk of delays, resistance, and ethical concerns.

## Conclusion

- **Adaptive design can offer many advantages, but careful planning is required to maximize successful implementation.** It is intended to improve the research process from its initiation, not to rescue already-failing studies.
- **Threats to study integrity and validity can jeopardize future product potential.** Prospective, prescriptive planning is crucial for avoiding bias and ensuring a strong design.
- **When AD is appropriate, straightforward, thorough, above-board approaches make it practical and more successful.** Proactive management of risk via simulations, independent data assistance and effective communication is essential.

## BIOS

### JOHN BALSER, Ph.D.
**President**

John Balser, President and co-founder of Veristat, has developed the company as an industry leader in the areas of clinical monitoring, data management, biostatistics, programming, medical writing and project management. John is actively involved with clinical projects in his role as one of Veristat's principal statistical consultants. In this role, he assists clients with clinical study design and program development based on his many years of experience in the statistical aspects of clinical research. He is often called upon to assist clients on a variety of statistical issues at meetings with regulatory agencies. Prior to founding Veristat in 1994, John served as Vice President, Biostatistics and Data Management at Medical & Technical Research Associates, Inc. He has held positions of increasing responsibility in the biostatistics departments at various pharmaceutical companies including E.R. Squibb, Biogen and Miles. John received his M.S. and Ph.D. in Biometrics from Cornell University, and has been actively engaged in clinical biostatistics for over 25 years.

### MARK CHANG, Ph.D.
**Senior Vice President, Strategic Statistical Consulting**

Mark Chang, Ph.D., applies his 20 years of experience as a statistician at both biopharmaceutical firms and CROs to excel in his role as a strategic statistical consultant. He is experienced with NDA submissions and working collaboratively with regulatory agencies throughout the clinical trial and submission process. Dr. Chang is also an adaptive design expert, having published eight books on biostatistics and adaptive clinical trial designs.

Dr. Chang is a fellow of the American Statistical Association and an adjunct professor of Biostatistics at Boston University. He is a co-founder of the International Society for Biopharmaceutical Statistics, co-chair of the Biotechnology Industry Organization (BIO) Adaptive Design Working Group, and a member of the Multiregional Clinical Trial (MRCT) Expert Group.

Dr. Chang received his Ph.D. in Civil Engineering and his Masters of Science in Biostatistics at the University of Massachusetts in Amherst, MA. He also received his Masters of Science and Bachelors of Science degrees at Hohai University in Nanjing, China.

### ROBIN BLISS, Ph.D.
**Director, Biostatistics**

Robin is a Director of Biostatistics at Veristat. She oversees the operations of the biostatistics department and collaborates with all integrated operational teams throughout the clinical trial and regulatory submission process to help produce high quality statistical deliverables.

Robin has over 12 years of experience in clinical biostatistics and is skilled in designing and implementing adaptive clinical trials. She has worked with both the United States Food and Drug Administration (FDA) and Japan's Pharmaceutical and Medical Devices Agency (PMDA) to defend adaptive design trials for clients. Her knowledge and expertise span a broad range of therapeutic and product indications including oncology, rare diseases, vaccines and devices/diagnostics. Throughout her career, Robin has participated in over 30 publications and continues to provide peer review for a variety of organizations. She earned her Ph.D. and M.A. from Boston University and her B.A. in Mathematics from Williams College in Williamstown, MA.

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