UNDERSTANDING ADAPTIVE DESIGNS FOR CLINICAL TRIALS

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WHAT IS ADAPTIVE DESIGN?

Adaptive design, as defined by the U.S. FDA, is "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."[1] Adaptive design characteristics include modifying an ongoing clinical trial in accordance with predetermined rules, based on data from interim analyses. Adaptive design allows for greater flexibility in clinical trials with benefits of adaptive design trials, or adaptive clinical trials (ACTs), including increased efficiency, better ethical protections, greater generalizability/understanding of drug effects and higher approval from sponsors. Overall, adaptive designs make better use of resources when conducting clinical trials.

HISTORY AND CURRENT APPLICATION OF ADAPTIVE DESIGNS

In December 2016, the United States Congress passed the 21st Century Cures Act to facilitate patient access to available treatments by bringing products to market faster. The act modified the U.S. FDA drug approval process and instructed the FDA to update its guidance on adaptive designs for clinical trials.

Although the 21st Century Cures Act refers to adaptive designs as novel methods that can enhance trial efficiency and lead to better research outcomes, and although some of these designs are new developments, adaptive designs found their way into biostatistics literature in the 1960s and 1970s. Due to implementation and interpretation challenges, however,

adaptive designs were rarely used and application to clinical trials did not occur until the 1990s[2]. Even with some acceptance within the pharmaceutical and biotech industry, to date, randomized controlled trials (RCTs) remain the gold standard in clinical research, and challenges to ACTs have delayed their adoption despite their multitude of advantages.

CONCERNS REGARDING ADAPTIVE DESIGNS

Concerns regarding adaptive designs in clinical trials that have hindered their use include inexperience, fears from stakeholders and regulatory bodies and practical limitations and challenges of some adaptive design types.[3]

- ***Inexperience:***
  Inexperienced researchers do not understand the added complexities of adaptive designs. Knowing when or when not to adapt a trial, how to strategically plan for logistical challenges and how to conduct complicated interpretations are skills of the expert biostatistician, not the novice.

1. U. S. Food and Drug Administration. Center for Drug Evaluation and Research. (2019). Adaptive Designs for Clinical Trials of Drugs and Biologics. Guidance for Industry. Retrieved from https://www.fda.gov/media/78495/download
2. Bothwell, L. E., Avorn, J., Khan, N. F., & Kesselheim, A. S. (2018). Adaptive design clinical trials: a review of the literature and ClinicalTrials.gov. BMJ open, 8(2), e018320. doi:10.1136/bmjopen-2017-018320
3. Pallmann, P., Bedding, A. W., Choodari-Oskooei, B., Dimairo, M., Flight, L., Hampson, L. V., … Jaki, T. (2018). Adaptive designs in clinical trials: why use them, and how to run and report them. BMC medicine, 16(1), 29. doi:10.1186/s12916-018-1017-7

- ***Fears from stakeholders and regulators:*** Changing rules in an ongoing trial creates complications and uncertainty, which can be intimidating to stakeholders and regulators. Lack of familiarity with new methods leads to conservative decision making (e.g., choosing familiar RCTs over ACTs).
- ***Practical limitations/challenges:*** Practical limitations are possible and challenges do exist. Special analytical methods are required to avoid increased chances of erroneous conclusions and bias, and for some design types, methods are not available to account for these increases. Efficacy gains can cause losses in other areas of a trial. Designing an adaptive trial takes more time than designing a traditional RCT, which can delay study start timelines. By adding modifications, logistical challenges arise in order to ensure trial conduct and integrity are preserved. Results gained from adaptive trials can be too specific to generalize, or lead to interpretability challenges.

ADDRESSING ADAPTIVE DESIGN CHALLENGES

To address the challenges associated with adaptive designs, the FDA suggests considering the following four principles during the clinical trial design stage:

- Control for the chance of erroneous conclusions by addressing possible Type I error probability inflation. Statistical theory can be utilized as well as simulations that evaluate the chance of erroneous conclusions.

- Bias in estimating treatment effects should be evaluated and available methods for adjusting estimates should be applied to reduce or remove bias whenever possible. If methods are unavailable, appropriate cautions to interpretation should be noted.
- Adaptive design trial details should be pre-specified prior to trial conduct, and documented in the study protocol. It is important that all adaptions be completely specified to ensure trial integrity, maintain safety, minimize access to comparative interim data and control for erroneous conclusions.
- Trial conduct and integrity should be maintained by predicting, and setting up safeguards to prevent, possible trial conduct issues. Controlled access to information should be addressed in this plan.

SUCCESSFUL CLINICAL TRIAL EXAMPLES USING ADAPTIVE DESIGN

Adaptive design modifications can be applied across all phases of a clinical trial and to numerous aspects of the trial design, including but not limited to, dose, hypothesis, study endpoints, treatment arms and sample size. Amarex's biostatisticians have successfully designed and conducted many adaptive design clinical trials, and NSF's investment will allow Amarex to do even more adaptive trial work. The following examples highlight our expertise and experience, having applied adaptions leading to efficacious outcomes for study sponsors:

- Six different adaptive clinical trials using sample size re-assessment for indications including diabetic foot ulcer (DFU), venous leg ulcer (VLU), hot flashes, schizophrenia, weight loss and pain management. Many of these products went on to obtain market approval.
- An adaptive clinical trial with modification to treatment arms (i.e., dropping an arm), with market approval pending for treatment of benign prostatic hyperplasia.

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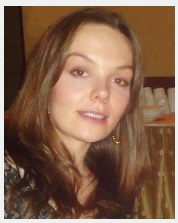
TAKE-HOME MESSAGE AND REGULATORY CONSIDERATIONS

- Adaptive designs offer innovative solutions to the rigidity of classically fixed, randomized controlled trials. Troubleshooting through modifications during the ongoing clinical trial process leads to study results that are informative and efficient, with increased ethical protection to participants while maximizing utilization of resources.
- Adaptive designs are complex, but challenges and complexities can be overcome with the help of experienced biostatisticians, consulting on the clinical trial from design through study completion.

Lastly, consider the role that regulatory bodies play in facilitating clinical trial product development. Agencies such as the FDA have indicated increasing interest in adaptive designs, and they are here to help you through this process. The FDA encourages sponsors to explore a number of design options, discussing considerations with the appropriate FDA review division. FDA notes its role will be more extensive on later phase adaptive clinical trials and minimal on early-phase exploratory trial designs. An FDA evaluation will be enhanced by thorough documentation of adaptive design plans and thorough documentation of study evaluations and reporting of trial results.

ABOUT THE AUTHORS

Hana Mekonnen has more than 15 years of experience in research and pharmaceutical product development as a biostatistician. She has worked on multiple ISS and ISE reports that have been submitted to the U.S. FDA for drug approvals, and she has been present at a number of FDA meetings to defend the statistical analyses presented. Hana earned her master's degree in statistics from Columbia University.



Deborah Cole has more than 10 years of experience in research and pharmaceutical product development, working in an administrative capacity. She has generated, updated and finalized various technical and non-technical documents for several clinical research departments. Deborah earned her master's degree in clinical psychology from Loyola University Maryland.

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