DATA

Introduction

Modern clinical trials are increasingly complex, with oncology studies typically having the most complex designs (Getz, 2022). Driven by this, Phase III trials collect, on average, 3.6 million data points, a sevenfold increase in volume from 20 years ago (Tufts CSDD, 2021), and while the cost of drug development has skyrocketed over the past few decades, this has not translated to greater success rates in clinical trials and drug approvals.

Therefore, it is not surprising that the industry has increased interest in flexible trial designs—such as adaptive ones—that can potentially expedite trials' timeline and enhance the likelihood that it will answer the question it was designed to address. This includes stopping a trial early for futility, which can be viewed as a success because the research question has presumably been answered; resources can then be reallocated to more promising programs (Bothwell, 2018; Hummell, 2015). These possible outcomes benefit patients and sponsors alike.

Adaptive designs differ from traditional fixed-sample designs. They use accumulating data while the study is ongoing to make prespecified changes (i.e., adaptations) that may, for example, provide the flexibility to identify the clinical benefit of a treatment during a trial, and then apply that information to patients enrolling in the trial without undermining its scientific validity and integrity (Madhavan, 2021; Chow, 2014; Menis, 2014; Berry, 2012; Gallo, 2006; Pallmann, 2018; Zang, 2014). Each adaptive design is unique, and they are applicable to both exploratory and confirmatory clinical trials (Bhatt, 2016). Both industry groups and regulators encourage the use of adaptive designs. Both have published documents discussing methods, strategies, and best practices when implementing an adaptive design (Gallo, 2006; EMA, 2007; FDA, 2019).

This white paper provides a brief introduction to adaptive designs, including their major benefits and challenges and best practices for operationalizing them. This foundation will help maximize the likelihood of success when implementing an adaptive trial design.

What Is an Adaptive Design?

In their 2019 Guidance titled Adaptive Design Clinical Trials for Drugs and Biologics Guidance for Industry, the FDA defines an adaptive design as the following:

Generally, adaptive designs are recognized for their potential to improve study power, reduce sample size, lower total cost, exploit biomarker profiles to identify efficacious drugs for subgroups of patients and shorten the time for drug development.

In contrast to traditional fixed-sample (nonadaptive) designs, these trials allow for the review of data at a prespecified point(s) during the study. This information may then be used to inform predefined adaptations to key parameters while maintaining trial integrity and outcome validity (Figure 1) (Krendyukov, 2021; Madhavan, 2021; Chow, 2014; Menis, 2014; Berry, 2012; Gallo, 2006). The growing interest in adaptive designs is driven by their capacity to maximize outcomes and insights toward efficacy while minimizing safety impacts on patients. Another major benefit is minimizing patient numbers yet still achieving sufficient statistical power to make a conclusion.

Figure 1: Depiction of a Traditional Fixed-Sample Design Compared to an Adaptive Trial Design

Adapted from Pallmann, P. et al. Adaptive designs in clinical trials: why use them, and how to run and report them. BMC Medicine (2018) 16:29. Available at https://doi.

Figure 2: Summary of different types of adaptive designs for clinical trials.

From Kairalla et al. Adaptive trial designs: a review of barriers and opportunities. Trials (2012);13(1), 1-9. Available at https://trialsjournal.biomedcentral.com/

Table 1 provides a descriptive summary of major design methods and terminology commonly used in adaptive design trials.

Table 1: Major design methods and terminology commonly employed in adaptive clinical trials

ADAPTIVE TRIAL TYPES AND SPECIAL TOPICS	BRIEF DESCRIPTION
Group sequential design	P
Sample size	P

What is modi□ed?

Each adaptive design is unique, and the possible modi□cations depend on the design category (Figure 2); some of these have overlapping features, and others blend features from different possible designs (Kairalla, 2012; Bhatt, 2016; Rong, 2014).

Possible modi□cations include the following:

Trial procedures, eligibility criteria, abandoning treatments or doses, treatment duration, laboratory testing procedures, diagnostic procedures, criteria for evaluation and assessment of clinical responses; and

Statistical procedures, including randomization, study design, and hypotheses, study endpoints, re□ning sample size, including changing treatment arm ratios, data monitoring and interim analysis (which may stop a trial for lack of ef□cacy), statistical analysis plan, and/or data analysis methods.

Industry and Regulatory Acceptance of Adaptive Designs

Adaptive designs are well established, with group sequential designs being used for decades (Rong, 2014). An estimate by the Tufts Center for the Study of Drug Development indicated that across the industry, simple adaptive designs were being used in roughly 20% of clinical trials (CSDD, 2013). Their adoption continues to grow as industry and regulators further gain experience and expertise. According to one study, adaptive trials were found to have reached "established status," although they are a small proportion of all clinical trials. The study also found that **"drugs developed using adaptive trials included in this study had a Phase II/III likelihood of launch of 81 sduserthere well e/ included in**

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