MEDIDATA

WHITE PAPER

Adaptive Designs Save Time and Money

Why Aren't They Used More Often?

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:

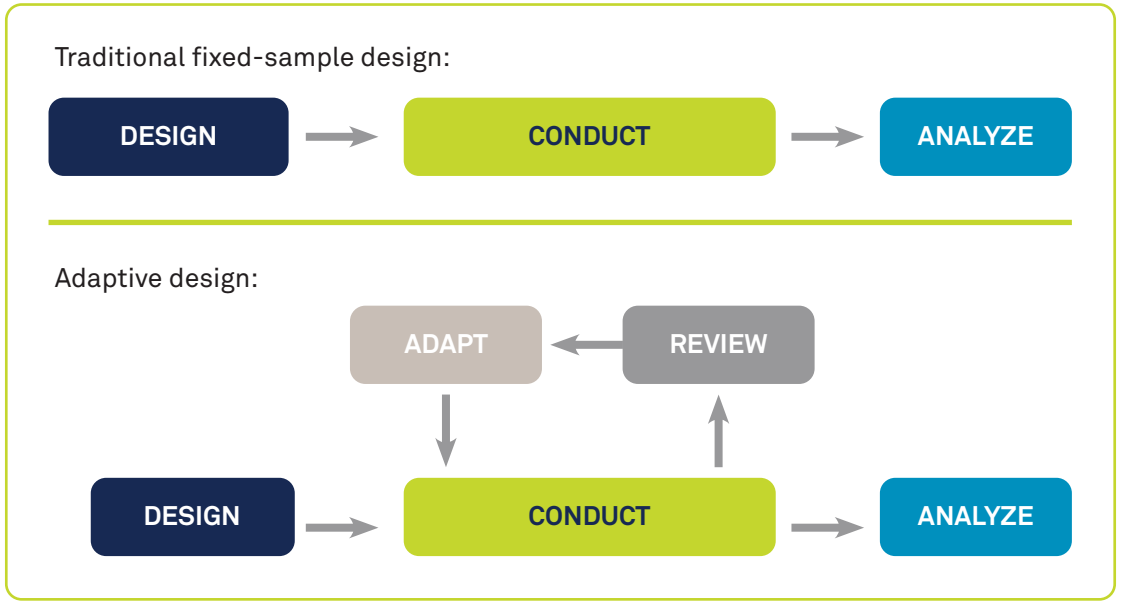
> **"a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in that trial." (FDA, 2019)**

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.

> **"An adaptive design is one in which the accumulating data are used to modify the trial's course. Adaptive designs are ideal for addressing many questions at once." (Berry, 2012)**

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.

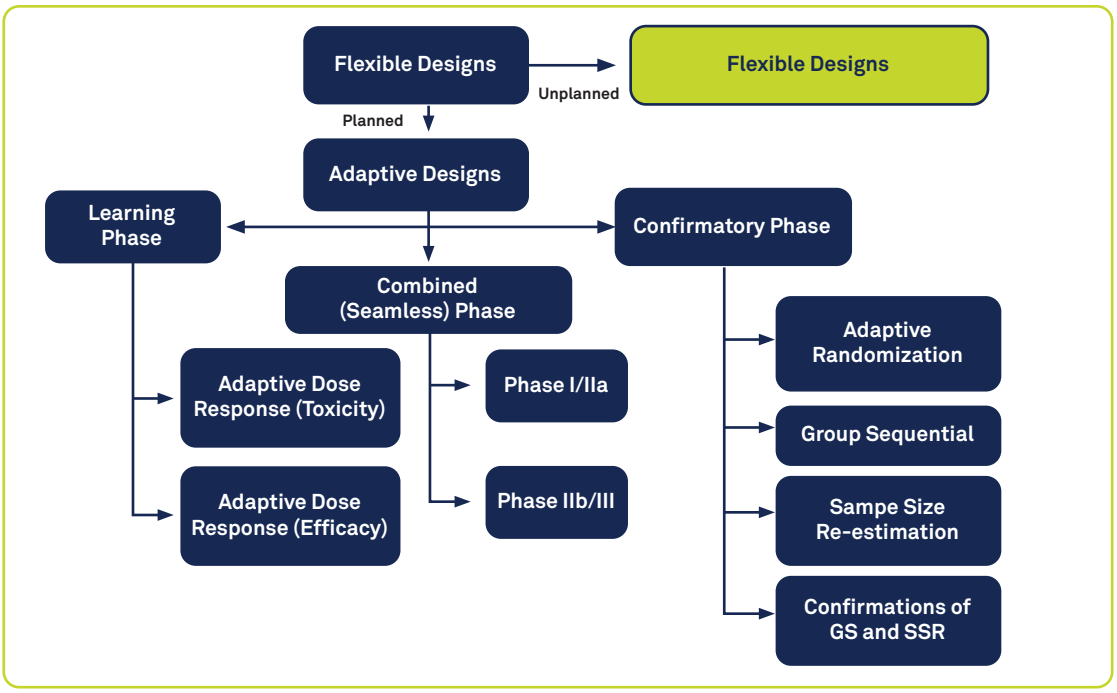
Figure 1: Depiction of a Traditional Fixed-Sample Design Compared to an Adaptive Trial Design



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.org/10.1186/s12916-018-1017-7. Used under Creative Commons Attribution 4.0 International License: https://creativecommons.org/licenses/by/4.0/

While adaptive designs are commonly aimed at creating a situation where a greater number of patients enter the potentially superior treatment group(s), another common type is a sample size re-estimation. This does not change the probability of randomizing a patient to a "superior" treatment but rather uses the existing efficacy data and the effect size to determine whether (1) the study is futile and (2) the planned enrollment is sufficient to produce the needed statistical power based on the projected effect size. Thus, it primarily focuses on identifying failure early and ensuring that the study is adequate to demonstrate a statistically significant effect, if one exists. Figure 2 summarizes different types of adaptive designs for clinical trials (Kairalla, 2012). Generally, adaptive designs tend to result in fewer clinical trials while achieving the desired outcomes, such as seamless Phase I/II and Phase II/III designs that have combined objectives, and doing it more cost-effectively because failed studies are terminated earlier.

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/articles/10.1186/1745-6215-13-145. Used under Creative Commons Attribution 2.0 Generic License: https://creativecommons.org/licenses/by/2.0/

Using adaptive designs during early-phase studies can help in planning later-phase trials, since they produce detailed information regarding patient response and tolerance to wider ranges of doses and treatment courses than is typical with traditional fixed-sample designs (FDA, 2019). This can lead to smaller sample sizes in confirmatory studies and eliminate ineffective treatment arms. For ongoing later-phase studies, interim data can be used to adapt the study based on new information. This can reduce the chances of a failed study or identify a futile study earlier.

As noted, adaptations must be preplanned and should be based on data from the ongoing study; because they were planned for and approved before the trial started, no downtime is expended waiting for approvals or de novo programming. In the trial planning phase, the FDA has highlighted the importance of modeling and trial simulations for comparing the performance of adaptive design trials under different scenarios and recommends estimating trial operating characteristics and demonstrating that these meet desired levels (FDA, 2019). Detailed trial simulation data should be submitted to the FDA to justify the adaptive trial's scientific credibility.

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	Prospective interim analysis with prespecified criteria for terminating the trial
Sample size	Prospectively planned modifications to the sample size based on interim estimates (e.g., unblinded sample size adaptation/ re-estimation)
Patient population (e.g., adaptive enrichment)	Adaptive modification of the patient population based on comparative interim results
Treatment arm selection (pick-the winner/ drop-the-loser, adaptive dose-ranging, etc.)	Adding or terminating arms (dropping the inferior treatment group(s), modifying treatment arms and/or adding additional arms; allocating more patients to treatment doses of interest, reducing the allocation of patients to doses that appear noninformative, etc.)
Patient allocation (randomization or treatment switching, etc.)	Adaptation based on either comparative baseline characteristics or comparative outcome data
Endpoint selection	Adaptive modification to the choice of primary endpoints based on comparative interim results
Seamless Phase II/III	Combined objectives (Phase II and III) moving from Phase II (investigational stage) to Phase III (efficacy or confirmatory) without stopping the patient enrollment process.
Biomarker adaptive	Adaptations based on an interim analysis of the treatment responses of biomarkers (can be used to select patient populations for subsequent trials or identify the natural course of a disease)
Multiple design features	Combination of two or more adaptive features (complex)
Special considerations and topics	• Bayesian design • Simulations in trial planning • Time-to event setting • Potential surrogate or intermediate endpoints • Secondary endpoints and safety considerations • Design changes/hypothesis change

**Table adapted from Krendyukov, A. et al. Value of Adaptive Trials and Surrogate Endpoints for Clinical Decision-Making in Rare Cancers. Front. Oncol., 08 March (2021). Available at https://www.frontiersin.org/articles/10.3389/fonc.2021.636561/full. Used under Creative Commons Attribution 4.0 International License: https://creativecommons.org/licenses/by/4.0/.*

What is modified?

Each adaptive design is unique, and the possible modifications 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 modifications 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, refining sample size, including changing treatment arm ratios, data monitoring and interim analysis (which may stop a trial for lack of efficacy), 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 percent,** which is 13 percentage points higher than the likelihood of launch of non-innovative trials" and, **on average, adaptive trials recruited faster than control (non-innovative trials),** and because adaptive trials can be designed to run across multiple phases, a longer recruitment time may still save time overall if one trial replaces several individual phase trials (Economist, 2018).

Adaptive designs are fully recognized and encouraged by regulators, including the FDA and EMEA (FDA, 2019; EMA, 2007). Oncology drugs have been approved on the basis of Phase I and II studies that employed enrichment strategies or expansion cohort strategies to address recruitment difficulties for rare types of cancers (e.g., vismodegib and crizotinib) (Menis, 2014). Furthermore, industry groups, such as the Pharmaceutical Research and Manufacturers of America (PhRMA) and Drug Information Association (DIA), and Congress-authorized groups such as The Patient-Centered Outcomes Research Institute (PCORI), have established adaptive design working group that put forth strategies, methods, and implementations to provide the best opportunity for broader usage and regulatory acceptance (Gallo, 2006; Rong, 2014; Detry, 2012; Miller, 2017). For instance, a publication by the DIA's Adaptive Design Scientific Working Group used case studies to highlight the practical use of adaptive designs that were deemed "less understood" by the FDA (which defined these as designs with limited regulatory experience), to encourage their appropriate use by industry (Miller, 2017). Overall, all stakeholders recognize the importance of achieving the desired trial objectives. From a regulatory perspective, none of the challenges are unique. The same processes must be followed, although it is important to focus on maintaining the blind (because data are analyzed at interim points).

Since adaptive designs are generally more complex than traditional fixed-sample designs, they often require higher levels of planning and expertise in disciplines such as statistics and simulation. However, with the appropriate up-front planning, they can play a key role in the success of drug development programs and reduce timelines (Printz, 2013).

Benefits of Adaptive Trial Designs

The following are some of the best-characterized benefits of adaptive trial designs:

- Improve study power
- Reduce sample sizes and total cost
- Avoid maintaining patients on ineffective doses or treatments
- Identify efficacious drugs for specific subgroups of patients based on biomarkers
- Shorten time for drug development by conducting multiple studies simultaneously
- Aid in planning for confirmatory phase studies
- Stop trials earlier to save resources and avoid exposing patients to ineffective and/or unsafe treatments

Challenges Associated with Adaptive Trial Designs

The following are some of the common challenges that should be taken into consideration while planning to use an adaptive trial design:

- Trial planning can take longer, and simulations often need to be run and submitted to regulators prior to study initiation
- A single individual trial may cost more, and studies often have more cost uncertainty
- Functional leads (on CRO and sponsor sides) may be unfamiliar with adaptive designs
- Study and site personnel may require more training and education
- A high volume of data is generated that requires more complex analyses
- Confidentiality of interim data must be ensured to maintain the validity of the results
- Operational and methodological complexities may increase

Advanced planning, including obtaining input from experts in the field, goes a long way in circumventing common pitfalls and providing the best opportunity for success. The following section provides several best practices to consider before designing an adaptive trial so that it can be operationalized successfully.

Best Practices for Operationalizing Adaptive Trial Designs

Planning and collaboration are important factors for any clinical trial but even more so for adaptive trials. This is because the operational planning for an adaptive study requires input from a multidisciplinary team, including the sponsor/CRO team, project managers, biostatisticians, modelers/simulators, programmers, clinical research coordinators, medical personnel, and regulatory affairs experts. The following are some of the key areas requiring collaboration and discussion:

- IT infrastructure, systems, roles, and processes all need to be modified and integrated to support the seamless execution of the interim analysis step, which is central to the adaptive process.
- Timing of adaptations requires careful consideration to avoid potential risks associated with adapting too early.
- Additional stakeholders, such as drug monitoring committees, must be integrated into the workflow. The integration process and stakeholder roles must be defined.
- Operational considerations related to drug supply management and inventory visibility are more critical due to the dynamic nature of adaptive trials.
- Forecasting and simulation of interim analysis decisions on clinical trial supply should be integrated into the process to understand risk and design trade-offs.

Planning, implementing, and managing the appropriate technologies are important steps of the planning process. Flexible randomization and trial supply management (RTSM) systems are essential components because they provide the ability to quickly and seamlessly implement multiple treatments and randomization scenarios with limited or no downtime or expensive change orders. Moreover, evaluating your electronic data capture (EDC) requirements is crucial, as adaptive designs can impact database design. Using a unified platform that combines EDC and RTSM systems is recommended as it minimizes programming, eliminates custom integrations, minimizes change orders with mid-study changes and provides almost real-time updates to randomization arms and inventory items once patient visits are recorded in the EDC system.

Medidata's RTSM and EDC solutions are unified and part of an integrated platform that is being used for adaptive trial design, conduct, and support. This unified solution eliminates double data entry, enables mid-study changes with no change orders and requires minimal reconciliation, expediting study start-up and closeout. Mid-study protocol amendments are managed so that sites or countries can be on different designs while awaiting regulatory approval without stopping enrollment.

Why Aren't Adaptive Designs Used More Often?

Since adaptive designs require careful planning by multidisciplinary teams, the lead time between initiating planning and starting the study can be longer compared to a traditional study. However, in our experience, the longer lead time is often offset by the advantages offered by a well-designed adaptive trial. It is also recognized that the FDA has expressed some concerns about biases that could be introduced into adaptive designs, ultimately undermining the study results (FDA, 2019). Therefore, it is absolutely critical to engage with experts in adaptive designs and with regulatory agencies as early as possible. This will provide the best opportunity that the adaptive design can be operationalized and that it will be accepted.

Lastly, adaptive designs often require a highly unified technology infrastructure with teams having the appropriate training to support the design. Early consultation with clinical trial technology experts, especially those with experience implementing adaptive designs on unified platforms, can further ensure your study will be accepted and successful.

Read our Syneos Health case study to learn more about how this global, full-service CRO used Medidata's Rave EDC and Rave RTSM solutions to support a complex adaptive trial protocol design, which allowed modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity.

Summary

Adaptive designs leverage accumulating results during a study to adapt the course of the trial. Adaptive designs can benefit both early and confirmatory studies, and with the appropriate level of upfront planning, these designs can result in fewer clinical trials while achieving the desired outcomes, and doing it more cost-effectively because failed studies are terminated earlier. Prior to embarking on an adaptive trial, it is highly advisable to hold early discussions with regulators and experts in adaptive designs, including experts with a deep understanding of what technological infrastructure should be in place so that your study is positioned for success.

Medidata has extensive experience with adaptive trial designs. Our multidisciplinary expert teams can help with the planning and implementation of your adaptive design, so that common challenges and pitfalls are circumvented.

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