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Adaptive Clinical Trial Designs: A Modern Approach

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Abstract: Randomised controlled trials (RCTs) remain the gold standard for evaluating clinical interventions, however, their traditional fixed designs are often resource-intensive, time consuming and ethically limited in the context of emerging therapies. Adaptive clinical trial designs have emerged as a robust alternative, offering pre specified flexibility that allows modifications based on interim data without compromising statistical validity. This article provides a comprehensive overview of adaptive clinical trial methodologies, including group sequential designs, sample size re estimation, response adaptive randomization, adaptive enrichment, seamless phase II/III designs, drop-the-loser approaches, master protocols (platform, basket and umbrella trials), hypothesis adaptive strategies and multiple adaptive designs. The methodological advantages of these approaches include improved efficiency, reduced patient exposure to ineffective treatments, enhanced ethical oversight and accelerated drug development timelines. The article further discusses operational considerations such as trial planning, simulation studies, data quality requirements and the role of independent monitoring committees in preserving trial integrity. Regulatory perspectives from the FDA, EMA and Philippine FDA are also reviewed, highlighting the importance of pre specification, control of type I error and early regulatory engagement. Evidence from key studies, including Bayesian re analyses of oncology trials and large-scale adaptive platforms during the COVID-19 pandemic, demonstrates the practical utility and efficiency gains of adaptive methodologies. Despite their advantages, adaptive designs introduce statistical and operational complexity, requiring rigorous planning and multidisciplinary coordination. Overall, adaptive clinical trials represent a transformative evolution in clinical research, enabling more efficient, ethical and data driven decision making in modern drug development.

Key Words: Adaptive Clinical Trials, Randomized Controlled Trial, Interim Analysis, Group Sequential Design, Sample Size Re Estimation, Response Adaptive Randomization, Adaptive Enrichment, Seamless Phase II/III Design, Master Protocols, Bayesian Methods, Clinical Trial Efficiency, Regulatory Guidance.

INTRODUCTION

Randomised controlled trials (RCTs) are widely acknowledged as the most reliable method for evaluating the efficacy of clinical interventions. Their methodological rigor and capacity to minimise bias make them the preferred evidence base for regulatory bodies when considering approval of new therapeutic agents.

Nonetheless, the execution of modern RCTs often entails considerable financial, temporal, and organisational demands, posing challenges to their feasibility in practice.

Adaptive designs in clinical trials offer a flexible framework to address emerging challenges by incorporating accumulating data into preplanned modifications. Interim analyses enable ongoing monitoring to mitigate risks such as underpowered studies, covariate imbalance and ethical concerns. In cases where treatments show equal efficacy or futility, adaptive designs allow early termination, conserving resources and minimizing unnecessary patient exposure. Jennison and Turnbull emphasize the value of such approaches, particularly the ability to stop trials for efficacy or futility, thereby reducing sample size and cost while maintaining ethical standards. Seamless phase 2/3 designs further enhance efficiency by permitting treatment or dose selection at interim analysis and integrating data across phases under a single protocol for final efficacy evaluation.

The execution of adaptive designs in clinical trials is complex, particularly in studies involving multiple drugs, biomarkers and patient populations. Successful implementation requires extensive upfront planning, cross functional coordination and clear communication of risks and benefits to operational staff. Statistical and operational simulations are essential to evaluate design performance, while timely, high quality data capture preferably through Electronic Data Capture systems is critical for decision making. To minimize bias, interim analyses should be conducted by independent bodies such as an ISC and reviewed by a DMC, with robust SOPs and experienced biostatisticians ensuring integrity. This paper highlights methodological advances, implementation strategies and operational challenges in early phase adaptive trials, illustrated through the BATTLE study case example.

HISTORY AND BACKGROUND

The FDA's Strategic Path Initiative (2004) introduced adaptive clinical trials to address high attrition rates and improve flexibility in drug development. Draft guidance on adaptive trial design followed in 2010 and in 2012 the President's Council of Advisors on Science and Technology recommended pilot projects exploring adaptive approval mechanisms and expanded accelerated approvals. In 2019, the FDA issued updated guidance on *Adaptive Design Clinical Trials for Drugs and Biologics*, reflecting methodological advances. Extending this approach, the FDA's Centre for Veterinary Medicine released guidance in 2021 on adaptive and innovative designs for new animal drug effectiveness studies.

OVERVIEW OF TRADITIONAL AND ADAPTIVE CLINICAL TRIAL METHODOLOGIES

Feature	Traditional Clinical Trial	Adaptive Clinical Trial
Design Flexibility	Fixed design parameters (sample size, endpoints, treatment arms) set before trial begins	Flexible allows pre specified modifications during the trial based on interim results
Interim Analysis	Rarely used; data typically analysed only at the end	Regular interim analyses guide decisions (e.g., stopping early, adjusting sample size, dropping/adding arms)
Efficiency	Less efficient; may require larger sample sizes and longer timelines	More efficient; can reduce costs, shorten timelines and minimize patient exposure to ineffective treatments
Complexity	Simpler to design, conduct and analyze	More complex; requires advanced statistical methods and careful planning to avoid bias
Regulatory Acceptance	Well-established and widely accepted by regulators	Increasingly accepted, but requires detailed justification and robust statistical planning
Risk of Bias	Lower risk since design is fixed	Higher risk if adaptations are not properly pre specified; potential inflation of Type I error
Examples of Adaptations	None (fixed design)	Sample size re-estimation, treatment arm modification, early stopping for efficacy/futility, adaptive randomization

Resource Use	May waste resources if trial continues despite clear futility	Better resource allocation; can stop early or redirect efforts based on interim findings
Popularity	Historically dominant approach	Growing use in Phase II/III trials, especially in oncology and cardiovascular research

Types of Adaptive Clinical Trials

Clinical trials are the cornerstone of evidence-based medicine, but traditional fixed designs often lack flexibility and can be inefficient. Adaptive clinical trials represent a paradigm shift, allowing modifications to trial procedures based on interim data while maintaining scientific validity and regulatory compliance. These designs improve efficiency, reduce costs and enhance ethical standards by minimizing patient exposure to ineffective treatments. They are particularly valuable in areas such as oncology, rare diseases, and vaccine development, where rapid decision making and precision targeting are essential.

1. Group Sequential Designs

Group sequential designs are among the most established adaptive methods. They involve pre specified interim analyses at defined points during the trial. Based on these analyses, the trial can be stopped early for efficacy if the treatment demonstrates overwhelming benefit, for futility if success is unlikely or for safety concerns.

Example: In cardiovascular drug trials, interim analyses may reveal strong efficacy signals, allowing early approval and patient access.

Advantages: Ethical efficiency, reduced costs and faster decision making.

Challenges: Requires careful planning to avoid inflating type I error rates.

2. Sample Size Re-Estimation

This design allows adjustment of the trials sample size mid-course, based on observed variance or effect size. It is particularly useful when initial assumptions are uncertain.

Example: Neurological trials often face unpredictable variability in patient responses re estimation ensures adequate statistical power.

Advantages: Prevents underpowered studies and avoids unnecessary recruitment.

Challenges: Must be pre specified to avoid bias and regulatory concerns.

3. Response Adaptive Randomization

Response adaptive randomization modifies the probability of assigning patients to treatment arms as data accumulates. Treatments showing better outcomes receive more patients, while weaker arms receive fewer.

Example: Rare disease trials, where patient numbers are limited, benefit from maximizing exposure to promising therapies.

Advantages: Improves ethical balance and patient benefit.

Challenges: Complex statistical modelling and potential delays in randomization adjustments.

4. Adaptive Enrichment Designs

Adaptive enrichment designs refine eligibility criteria during the trial to focus on subgroups most likely to benefit, often guided by biomarkers.

Example: Oncology trials targeting patients with specific genetic mutations (e.g., HER2-positive breast cancer).

Advantages: Increases likelihood of demonstrating efficacy in responsive populations.

Challenges: Risk of excluding broader patient populations and complicating generalizability.

5. Seamless Phase II/III Designs

Seamless designs combine exploratory (Phase II) and confirmatory (Phase III) stages into one continuous trial. Data from the exploratory stage informs the confirmatory stage without interruption.

Example: COVID-19 vaccine trials used seamless designs to accelerate development timelines.

Advantages: Saves time, reduces costs and avoids duplication.

Challenges: Requires robust statistical planning to maintain validity across phases.

6. Drop-the-Loser Designs

In multi-arm trials, ineffective treatments can be dropped mid trial, allowing resources to focus on promising therapies.

Example: Antibiotic development trials often test multiple candidates simultaneously, dropping ineffective ones early.

Advantages: Efficient use of resources and improved patient outcomes.

Challenges: Requires clear pre specified criteria for dropping arms.

7. Master Protocols (Platform, Basket and Umbrella Trials)

Master protocols provide a unified framework to test multiple therapies or disease subtypes under one overarching design.

Platform Trials: Evaluate several treatments within one disease area, with arms added or removed over time. Example: The RECOVERY trial during COVID-19 tested multiple therapies simultaneously.

Basket Trials: Test a single therapy across multiple diseases or genetic mutations. Example: Targeted oncology drugs tested across cancers with the same mutation.

Umbrella Trials: Assess multiple therapies within a single disease, stratified by biomarkers. Example: Lung cancer trials testing different drugs based on genetic subtypes.

Advantages: Highly efficient, flexible, and resource saving.

Challenges: Operational complexity and regulatory oversight.

8. Hypothesis-Adaptive Design

A **hypothesis-adaptive design** is a clinical trial design that allows modifications to the study hypothesis or endpoints based on interim analysis results. Unlike traditional trials, where the hypothesis remains fixed, this design provides flexibility to incorporate emerging evidence. For example, a trial may begin with a superiority hypothesis and later switch to a non-inferiority hypothesis if interim findings indicate comparable clinical benefit. Similarly, the primary endpoint may be changed to a more appropriate secondary endpoint when supported by interim data. This approach helps improve the scientific relevance and efficiency of the trial while maintaining its overall objectives.

Advantages:

- Increases trial relevance by aligning objectives with evolving evidence.
- Can salvage trials that might otherwise fail under rigid hypotheses.
- Provides flexibility to adapt to unexpected findings.

Disadvantages:

- Controversial in confirmatory Phase III trials, as changes may undermine credibility.
- Risk of introducing bias and complicating statistical interpretation.
- Regulatory agencies often view such changes with caution.

Example: A cardiovascular trial initially designed to test superiority of a new drug over standard therapy may switch to a non-inferiority hypothesis if interim results show the drug is equally effective but has fewer side effects. This adaptation allows the trial to remain meaningful and potentially support regulatory approval.

9. Multiple Adaptive Design

A multiple adaptive design combines two or more adaptive strategies within a single trial. For example, a study might integrate group sequential design (early stopping rules), drop the loser design (eliminating ineffective arms), and adaptive seamless Phase II/III design (combining phases). Another example is combining adaptive dose escalation with adaptive randomization. The goal is to maximize flexibility and efficiency, addressing multiple uncertainties simultaneously.

Advantages:

- Maximizes flexibility by incorporating several adaptive features.
- Streamlines drug development and reduces time.
- Optimizes resource use by adapting to multiple aspects (dose, patient population, endpoints).

Disadvantages:

- Statistical inference becomes highly complex when multiple adaptations are combined.
- Controlling type I error rates is difficult.
- Operational burden increases significantly, requiring advanced simulations and strong expertise.
- Regulatory agencies are cautious and demand strong justification.

Example: An oncology trial may use a multiple adaptive design by starting with dose escalation to identify safe ranges, applying drop the loser to eliminate ineffective doses and incorporating group sequential rules to stop early if strong efficacy or safety signals are observed. This combination accelerates development while ensuring patient safety and efficient resource use.

Regulatory Guidance for Adaptive Clinical Trial Design

Adaptive clinical trial designs depend on clear regulatory frameworks to protect scientific integrity and patient safety. A strong grasp of these guidelines is essential for successful implementation in the Philippines and worldwide.

FDA Guidance (United States): The U.S. Food and Drug Administration issued guidance in 2019 to support adaptive designs for drugs and biologics. It highlights the need for prospective planning to ensure trial validity, with particular emphasis on controlling type I error rates and applying rigorous statistical methods. The FDA encourages approaches such as Bayesian adaptive trials, seamless phase 2/3 designs, and adaptive dose finding strategies. Early engagement with regulators is recommended to clarify expectations and reduce uncertainty.

EMA Guidance (Europe): The European Medicines Agency, through its Committee for Medicinal Products for Human Use (CHMP), recognizes adaptive trials as valuable tools when pre specified adaptations are clearly defined. Examples include sample size re estimation, treatment arm modifications and changes in randomization ratios. The EMA stresses that adaptations must be scientifically justified and documented in advance, with early consultation advised to align trial objectives with regulatory standards.

Philippine Regulatory Context: The Philippine FDA follows international best practices, requiring adaptive trial protocols to meet ethical and scientific requirements. Protocols must detail interim analysis plans, adaptation decision rules and monitoring procedures. Ethical review boards play a central role in safeguarding patient welfare during trial modifications, while transparency in reporting adaptations is emphasized to maintain public confidence.

Global Harmonization Efforts: Global regulators including the FDA and EMA, are working toward harmonized standards for adaptive trials. Initiatives such as the International Council for Harmonisation (ICH) aim to streamline requirements across jurisdictions. Success in multinational trials depends on clear documentation, transparent adaptation rules, and proactive communication with regulators. For countries like the Philippines, alignment with these global standards enables participation in international research and accelerates access to innovative therapies.

Benefits of Participating in an Adaptive Clinical Trial

Participating in an adaptive clinical trial offers individuals access to innovative therapies that may not yet be available through standard medical practice. As these trials are designed to adapt based on accumulating

evidence, participants may have an increased chance of receiving treatments that show greater promise during the study. One of the key strengths of adaptive clinical trials is their patient-centred design.

As interim data are continuously evaluated, certain aspects of the trial can be adjusted to optimize treatment allocation. This approach may reduce the time participants spend on less effective therapies and, when scientifically justified, allow reassignment to treatment groups demonstrating more favourable outcomes. Adaptive trials also include ongoing monitoring of participants' health and therapeutic responses. This continuous evaluation supports a more individualized care experience, enabling healthcare professionals to make timely decisions based on changes in a participant's condition.

Participants also gain a better understanding of their disease and emerging treatment strategies. In addition to potential personal benefits, participation plays an important role in advancing medical research. Every participant contributes valuable clinical evidence that supports the development of safer and more effective treatments. These contributions not only benefit current patients but also help improve healthcare outcomes for future generations.

Risks of Participating in an Adaptive Clinical Trial

Although adaptive clinical trials offer several advantages, they also involve certain uncertainties that participants should carefully consider. Since these studies evaluate investigational treatments, the effectiveness and safety of the therapies being tested may not be fully established.

A unique feature of adaptive trials is that study procedures can change based on interim findings. While these modifications are intended to improve the trial's efficiency and scientific value, they may result in changes to a participant's treatment plan. As a result, interpreting the overall effectiveness of a particular treatment can become more complex.

Another important consideration is that new information about potential side effects or treatment related risks may emerge as the study progresses. Participants are therefore encouraged to remain informed throughout the trial so they can make well informed decisions about continuing their involvement.

To protect participant welfare, adaptive clinical trials are conducted under strict regulatory and ethical standards. Before a study begins, detailed protocols outlining all planned adaptations must receive regulatory approval. Independent Data Monitoring Committees (DMCs) regularly review safety data and monitor trial progress, ensuring that any necessary changes are scientifically justified and ethically appropriate. Additional safeguards include ongoing oversight by regulatory authorities, comprehensive informed consent procedures, adherence to Good Clinical Practice (GCP) guidelines and transparent reporting of study outcomes after the trial concludes.

EVIDENCE BASED EXAMPLES

1. Application of Bayesian Adaptive Decision-Theoretic Methods in a Three-Arm Exercise Oncology Trial¹⁰

The Physical Exercise during Adjuvant Chemotherapy Effectiveness Study (PACES) trial evaluated 230 breast cancer patients undergoing chemotherapy who were randomized to three groups: supervised resistance and aerobic exercise (On Track), home based physical activity (OncoMove), and usual care (UC). The trial data was retrospectively reanalysed using a Bayesian adaptive decision theoretic framework alongside a frequentist group sequential approach, incorporating interim analyses conducted after every 36 participants. The primary endpoint was chemotherapy treatment modifications (any vs. none). Results showed that treatment modifications occurred in 34% of patients in both the UC and OncoMove groups, compared with 12% in the On Track group ($P = 0.002$). Using the Bayesian-adaptive design, the OnTrack intervention was identified as the most effective arm after 72 patients in the “pick-the-winner” setting and between 72 and 180 patients in the “pick-all-treatments-superior-to-control” setting. In contrast, the frequentist group sequential design would have led to trial stopping after 180 patients, also demonstrating significantly fewer treatment modifications in the OnTrack group compared to usual care. Overall, the study demonstrated that a Bayesian adaptive decision theoretic approach can substantially reduce required sample sizes in multiarm clinical trials, particularly when using a “pick-the-winner” strategy.

2. Adaptive Clinical Trials During COVID-19 (2020)¹¹

In April 2020, the World Health Organization (WHO) launched the COVID-19 R&D Blueprint to accelerate global vaccine and treatment development through large, coordinated clinical trials. The plan proposed an international, randomized controlled trial system to rapidly evaluate multiple vaccine candidates in parallel and assess their safety and effectiveness within months of availability.

A key part of this effort was the Global Target Product Profile (TPP), which defined the desired features of COVID-19 vaccines. It categorized vaccines into two groups: those providing long-term protection for high-risk populations such as healthcare workers, and those offering rapid immunity to control new outbreaks.

The framework supported prioritizing promising vaccine candidates, tracking global development through a centralized “landscape” of trials and harmonizing late-stage clinical trial protocols. This enabled faster decision making and more efficient comparison of vaccine performance across countries.

At the same time, major adaptive trial platforms such as the WHO Solidarity trial, Europe’s Discovery trial and the U.S. led ACTT (Adaptive COVID-19 Treatment Trial) were used to evaluate COVID-19 treatments. These studies allowed researchers to modify trial designs based on emerging results, improving speed and efficiency in identifying effective therapies during the pandemic.

CONCLUSION

Adaptive clinical trial designs represent a significant advancement over traditional fixed randomized controlled trials by introducing flexibility while maintaining scientific rigor. These designs allow for pre-planned modifications based on interim data, improving efficiency and ethical conduct in clinical research. By enabling early stopping for efficacy or futility, adjusting sample sizes and refining patient populations, adaptive methods reduce unnecessary resource use and patient exposure to ineffective treatments. Their application in oncology, rare diseases and large-scale public health emergencies such as COVID-19 has demonstrated substantial practical benefits. However, the complexity of statistical planning, operational execution and regulatory compliance remains a key challenge. Robust pre-specification of adaptation rules, strong simulation studies and independent monitoring are essential to ensure validity. Regulatory agencies such as the FDA and EMA increasingly support these designs when properly justified and transparently implemented. Overall, adaptive clinical trials enhance decision making, accelerate drug development and improve the ethical and scientific quality of modern clinical research.

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