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The Evolution Of Clinical Trial Design And Its Implications On Regulatory Approval

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Abstract:
The evolution of clinical trial design is spurred by advancements in precision medicine, targeted therapies, and the requisite to address rare diseases. Traditional linear designs, while suitable for prevalent conditions, face limitations in the circumstance of rare diseases. Modern designs, such as adaptive trials, offer flexibility and efficiency in drug development. Regulatory bodies, like the Food and Drug Administration and European Medicines Agency, have reformed guidelines to accommodate these innovations, emphasizing careful planning, pre-specification, and controlled access to interim results to ensure trial integrity. Challenges include statistical complexities, ethical considerations, and regulatory harmonization. These challenges can be efficiently transcended by interdisciplinary collaboration, standardized guidelines, and ongoing dialogue among stakeholders. As the landscape continues to evolve, the successful implementation of novel trial designs requires robust infrastructure, resource management, and stakeholder collaboration. The pursuit of effective and efficient designs remains pivotal for expediting drug development, particularly for rare diseases, necessitating continued cooperation between the pharmaceutical industry and regulatory bodies. This article aims to gather information on the technical challenges and regulatory implications associated with the utilization of adaptive design in clinical trials.

Keywords: *Clinical Trial, Adaptive Clinical Trial, Precision Medicine, Rare Disease, Statistical Limitations; Technical Challenges*

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I. INTRODUCTION

The construction of clinical trial design requires a clear and specific research question and the outcome of the trial. The potential challenges are sample size, random, systemic or confounding bias, and type of disease, target population, type and duration of outcome but not limited to only these; should be considered during the design of clinical trial. Though there are different study designs like case-control or cohort; the common trial designs used are placebo-control trials, factorial, cross over and randomized trials in clinical research and pharmaceutical industry. [(1)]

The traditional design of clinical trials is framed to be carried out in a continuous linear process (Phase I-IV) with systematic increase in study subjects while the evolving clinical trial designs deviate from traditional design in the aspect of sample size, recruitment strategy, interim analysis, statistical methods, etc. [(2)] Evolution of precision medicine with development of targeted therapy, molecular phenotyping, genomic and biomarker profiling has led to continuing modification in design of clinical trials. Though new clinical trial designs are complex they have certain predictable benefits like augmented drug development and evaluation, efficient use of resources, limited trial participants and abridge the entire clinical research process. [(3, 4)]

Traditional study designs are relatively congruous for the clinical research that focuses on prevalent and chronic diseases such as cardiac diseases, diabetes or psychiatric conditions. The design of clinical trial demands a constant revision and adaptation depending on the nature of the disease. The shift of focus on drug development and clinical trials of rare diseases demand a persistent enhancement of clinical trial design which is challenging. Innovation and modification of trail design is particularly due to the key factor that the patient population with rare diseases are smaller. [(5)]

There are many newer study designs that are reported including two-way enriched design, adaptive design (AD), master protocol, basket design, umbrella design and platform design and more other study specific designs are evolving. [(4, 6, 7)] The advancement in technology, computational tools, clinical trial conduct and the innovations in therapeutic drugs require optimization of clinical trial design specific to the study. The changing landscape of clinical trial designs has led to regulatory considerations, prompting revisions to the guidelines.

II. NEED FOR CLINICAL TRIAL DESIGN EVOLUTION

Traditional linear clinical trial designs have certain limitations that impact the final outcome and analysis of a trial. Randomized control trials (RCT) are considered to be the golden standard by reducing the risk of bias and used in clinical trials. Due to the credibility of randomized trial they are reported in custom to make policy decisions. However, the potential elements of RCTs that can result in bias or exaggerate intervention effect evaluation are sequence generation, allocation concealment and blinding. A systematic review found that inadequate sequence generation or allocation concealment can exaggerate intervention estimates, while unblended trials may overstate subjective outcomes and increase between-trial heterogeneity without double blinding. [(8)]

Another limitation is the power and sample size of the trial. A study found that only half of the reported sample size calculations of randomized trial were reproducible (53%), with 12% of trials producing a larger sample size than reported. Additionally, 25% of trials did not provide enough information for replication. Most studies failed to compute anticipated attrition or standard deviation, which can significantly impact a trial's ability to detect a meaningful treatment difference. [(9)]

III. MODERN CLINICAL TRIAL DESIGNS

The Modern or innovative clinical trial designs possess a common element known as interim analysis. The key principles of adaptive clinical trials are [(10)]

Manoeuvre the Chance of Erroneous Conclusions

Adaptive designs like group sequential designs may increase Type I error probability due to multiple statistical hypothesis tests. Hence statistical methods to determine appropriate significance levels for interim and final analyses should be deliberately considered ensuring overall Type I error control. Bayesian adaptive designs may require simulations to evaluate the risk of erroneous conclusions.

Estimating Treatment Effects

Some adaptive designs can introduce bias in treatment effect estimates, affecting primary and secondary endpoints but diverse methods may exist for adjusting estimates to reduce bias.

Trial Planning

Details of adaptive designs must be completely specified before the trial begins, including the number and timing of interim analyses, adaptation type, inferential methods, and decision algorithms. Complete pre-specification is vital for feasible statistical methods, confidence in unbiased adaptations, and prevention of unplanned decision-making based on accumulated knowledge.

Maintaining Trial Conduct and Integrity

Adaptive designs can complicate trial conduct, influencing sponsor, investigator, and participant behaviour. Access to comparative interim results should be restricted to individuals with relevant expertise, independent of those conducting the trial, knowledge of which could assist in interpretation of the results and impact trial success.

Methodological advancements in clinical trial design are instrumental in the era of precision medicine. They facilitate the development of therapies that are tailored to the unique genetic and molecular characteristics of individual patients, increasing the likelihood of therapeutic success and reducing the risk of adverse effects.

The most prevalent type of adaptation in clinical trial designs is the seamless phase II/III design, accounting for 23.1% of the cases. It is followed by adaptive dose progression (19.2%), pick the winner/drop the loser (16.7%), sample size re-estimation (10.3%), change in the study objective (9.0%), adaptive sequential design (9.0%), adaptive randomization (6.4%), biomarker adaptive design (3.8%), and endpoint adaptation (2.6%). [(11)] In this article we have listed the examples of different types of adaptive clinical trial designs (Table 1) that contribute to a more efficient drug development process, ultimately improving patient care and outcomes.

Table 1 : Types of Adaptive Clinical Trial Designs

Study Design	Study Conducted	Disease condition
Master Protocol - Basket Design [(12)]	Antitumor response of Ado-trastuzumab emtasine in different HER2-amplified or mutant cancers	Advanced lung, endometrial, ovarian, bladder, colorectal, and other cancers
Master Protocol - Umbrella Design [(12)]	plasmaMATCH evaluated 5 different therapies for advanced breast cancer	Breast Cancer
Bayesian approach – Two Arm Design [(13)]	CLARITY trial comparing angiotensin receptor blockers together with standard care to standard care alone in reducing severity	COVID-19
Bayesian approach – Group Sequential Design	OSCAR trial comparing high frequency oscillatory ventilation to conventional positive	Acute Respiratory Distress Syndrome

[13]	pressure ventilation	
Bayesian approach – Dropping Arm Design [13]	CATALYST study comparing namilumab or infliximab to standard care in hospitalized	COVID-19
Bayesian approach – Response Adaptive Randomization [13]	endTB trial investigating efficacy of five new treatment regimens and a control	Multidrug-resistant tuberculosis
Interventional Randomized Controlled Trial [14]	SOLIDARITY trial to evaluate efficacy of artesunate, infliximab and imatinib in addition to the local standard of care	COVID-19
Adaptive Platform Trial [15]	RECOVERY trial comparing dexamethasone, hydroxychloroquine, lopinavir-ritonavir or azithromycin with standard of care	COVID-19

IV. TRANSFORMATION OF REGULATORY GUIDELINES FOR MODERN CLINICAL TRIAL DESIGNS

Accounting to the amplification of type I error in the event of early termination of trial data monitor committee (DMC) was established to monitor the accruing clinical trial data for safety and efficacy. It was in 1998 ICH-E9 was issued that states sample size modification can be with the trial with continuous blinding of the subjects and the protocol amendment and significance should be reported. Later in 1998, United States Food and Drug Administration (US FDA) published the early guidance draft for adaptive trial designs. [16]

Regulatory bodies provide pathways for expedite drug development and approval for novel therapies. In 2014, the EMA initiated a trial adaptive pathways program with the aim of generating significant trial outcomes for rare diseases. Following an evaluation of the program, in 2016, they made the decision to officially implement it. [5]

The adaptive trial guidance for drugs and biologics was published by FDA in 2019 that outlines key principles for planning, executing, and reporting outcomes in adaptive clinical trials. Additionally, it offers advice to sponsors on the necessary information to submit for FDA assessment of such trials, encompassing Bayesian adaptive methods and complex trials utilizing computer simulations in their design. According to FDA when submitting documentation for a clinical trial with an adaptive design, the following key components should be included to facilitate a thorough evaluation: [10]

- *Rationale for the Selected Design:* Provide a rationale for the chosen adaptive design to compare operating characteristics with alternative designs.
- *Detailed Adaptation Plan:* Include a thorough description of the adaptation plan, specifying the number and interval of interim analyses, aspects of the design modification, and the decision rule for adaptations.
- *Roles of Implementation Bodies:* Clearly outline the roles of bodies responsible for implementing the adaptive design, such as the Independent Data Monitoring Committee (IDMC) or other committee if applicable.
- *Pre-specified Statistical Methods:* Pre-specify statistical methods for producing interim results, guiding adaptations, conducting hypothesis tests, and estimating treatment effects. If using novel software, provide sufficient details on quality test reports and other such documents to avoid ambiguity.
- *Evaluation of Operating Characteristics:* Conduct evaluations of design operating characteristics, covering Type I error probability, power, expected, sample size, bias in treatment effect estimates, and confidence interval coverage using analytical calculations and/or simulations for this evaluation.
- *Simulation Report (if applicable):* If simulations are the primary evaluation method, submit a detailed report including an overview of the trial design, example trials, parameter configurations, the number of simulated trials, simulation results, and simulation code. Ensure readability, comments, and inclusion of random seeds.
- *Data Access Plan:* Present a comprehensive data access plan detailing how trial integrity will be maintained during adaptations. Include information on personnel performing interim analyses, controlling access to results, making adaptive decisions, and disseminating information. Establish procedures for compliance evaluation and document interim committee meetings.

This comprehensive documentation ensures that the FDA can thoroughly evaluate the trial design, understand the decision-making process, and verify the integrity of the data throughout the adaptive clinical trial.

The FDA also issued a comprehensive guidance to the industry regarding the appropriate utilization and integration of real-world data for the submission of investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) for regulatory decisions in 2022. But trail design consideration to use RWD in externally controlled trail is drafted by FDA in 2013 and not finalised. In externally controlled trial, the results of individuals receiving the experimental treatment as per the protocol are

contrasted with the outcomes of a separate group of individuals external to the trial that did not undergo the treatment or involved in the clinical trial. [10]

The regulatory recommendations (E20 EWG) for the design, implementation, analysis, and interpretation of adaptive clinical trials were proposed by ICH in 2018, with a strategic goal of finalizing the guideline by 2025. [17]

V. LIMITATIONS OF ADAPTIVE TRIALS

The use of Adaptive Design in clinical trials involves modifying analytical and statistical procedures based on interim data, and it has been a common practice in clinical research for several years. However, concerns are raised regarding the reliability of the statistical measures, such as p-values and confidence intervals, when using AD. Therefore, while AD offers advantages, it must be implemented with caution to maintain the integrity and validity of clinical research.

From a regulatory standpoint, the FDA is generally supportive of Adaptive Design in clinical trials, but there are ongoing efforts to define appropriate implementation. Rejections of protocols using such methods can lead to approval delays. The limited experience, both within the pharmaceutical industry and regulatory authorities, may result in difficulties regarding the scientific validity of adaptive testing, mainly due to the absence of universally accepted statistical methods for all possible adaptations. This lack of standardization can make it difficult, if not impossible, to produce clear statistical inferences during the regulatory approval process.

There is a common distress that using interim analyses for design adjustments might introduce bias and compromise the statistical validity of the clinical trial. However, as experience with AD accumulates, this anxiety tends to diminish. To mitigate such concerns, standard procedures for concealing interim results should be established before the trial commences. [11]

The implementation and conduct of an adaptive trial come with challenges that require careful consideration:

Robust Infrastructure*:* A robust infrastructure is a fundamental requirement for the proper execution of AD. This encompasses effective coordination and monitoring involving all stakeholders, including the sponsor, patients, and the investigative team, all of whom should possess a thorough grasp of the principles underlying AD.

Resource Challenges*:* Modifications made during the course of the trial, including adjustments to sample size, objectives, endpoints, or reference values, can present logistical complexities. These alterations can influence various aspects, such as the accessibility of physical resources (including space and additional procedures), the need for extra equipment, budget considerations (to accommodate additional costs related to extra procedures for patients), staffing requirements (possibly necessitating an expansion of the research team), and the utilization of statistical tools that can affect the quality of the test results.

Supply Challenge*:* Different forms of adaptations, like discontinuing treatment arms or doses, reallocating a higher number of patients to particular treatment arms, or recalculating the overall sample size following an interim analysis, can create difficulties in adequately coordinating the distribution of the experimental drug to all study centres. [11]

Between 2007 and 2012 there were 59 occurrences where scientific advice was sought by EMA for adaptive study designs in phase II and phase III clinical trials. These designs were primarily intended for confirmatory phase III or phase II/III studies. The most commonly proposed adaptations included reassessing sample sizes, discontinuing certain treatment arms, and enriching the study population. Notably, 20% of the 59 proposals for adaptive clinical trials were rejected, while the majority of proposals were either accepted (25%) or conditionally accepted (54%). (18)

VI. CHALLENGES AND CONSIDERATIONS IN NOVEL CLINICAL TRIAL DESIGNS

Clinical trials are experiencing a paradigm shift with the adoption of novel designs, ushering in innovation but also presenting a spectrum of challenges. This section critically dissects the multifaceted challenges associated with these new trial methodologies, ensuring a holistic understanding of the hurdles encountered in their implementation.

- ***Statistical Complexities:*** The integration of novel trial designs introduces statistical intricacies that demand careful consideration. Adaptive designs, for instance, involve real-time modifications based on accumulating data, necessitating advanced statistical methods. The article scrutinizes the complexities arising from interim analyses, sample size adjustments, and the potential impact on trial integrity. Statistical challenges extend to platform trials, where the dynamic nature requires sophisticated statistical modelling to accommodate multiple interventions and patient subgroups.
- ***Ethical Considerations****:* Innovative trial designs often intersect with ethical dilemmas, requiring a delicate balance between scientific rigor and patient welfare. The article examines the ethical implications of adaptive designs, particularly the need for transparent communication with trial participants regarding

potential changes to study protocols. It also delves into ethical considerations in basket trials, where a single treatment targets diverse molecular abnormalities, raising questions about equitable access and informed consent across varied patient populations.

- ***Regulatory Harmonization:*** Achieving consistency and alignment across diverse regulatory frameworks globally is a formidable challenge. The article investigates the hurdles in regulatory harmonization, where different health authorities may interpret and evaluate novel trial designs differently. It explores the need for standardized guidelines that facilitate a harmonized approach to regulatory approval. The discussion extends to the evolving role of regulatory agencies in adapting to innovative designs, ensuring that the approval process remains robust and reliable.

VII. FOSTERING CRITICAL DIALOGUE

The article emphasizes the necessity of fostering a critical dialogue surrounding these challenges. It encourages a collaborative discourse among researchers, clinicians, ethicists, and regulatory professionals to collectively address the identified hurdles. By fostering an open dialogue, the article envisions a pathway toward refining and optimizing novel trial designs, ensuring that ethical considerations are upheld, statistical complexities are navigated effectively, and regulatory harmonization becomes an achievable goal.

In essence, this section provides a nuanced examination of the challenges associated with novel trial designs, acknowledging their complexity while advocating for collaborative efforts to overcome these hurdles. By addressing statistical intricacies, ethical considerations, and regulatory harmonization, the article contributes to the ongoing discourse on the future trajectory of clinical trial design.

VIII. CONCLUSION

The evolution of clinical trial design reflects the dynamic nature of medical research, driven by advances in technology, precision medicine, and the need to address rare diseases. Modern clinical trial designs, such as adaptive trials, have emerged to address the limitations of traditional linear trial designs. These new designs, with their focus on interim analysis and adaptability, hold great promise in expediting drug development and improving patient outcomes.

Regulatory bodies, like the FDA and EMA, have recognized the importance of adapting their guidelines to standardize these innovative trial designs. Periodical revision of regulatory guidelines recommends careful planning, adherence to pre-specification and limiting access to interim results to ensure the reliability and integrity of adaptive clinical trials. In unforeseen circumstances, any potential design changes should be discussed with the regulatory bodies.

The success of these modern trial designs relies on robust infrastructure, careful resource management, and effective collaboration among all stakeholders. As experience with adaptive trials accumulates, concerns about bias and statistical validity are expected to diminish, provided that standard procedures for concealing interim results are established.

In this ever-evolving landscape of clinical research, the pursuit of more effective and efficient clinical trial designs is essential to bring life-changing therapies to patients. As regulatory guidelines continue to evolve, the pharmaceutical industry and research community must work together to competently exercise the innovative clinical trial designs for their potential benefit of accelerated drug development and approval process, especially for rare diseases.

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