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Review Article

Clinical trial designs: a simplified overview

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ABSTRACT

Clinical trials aim to invent new, better, safer, more effective ways to prevent, detect, or treat health conditions and to compare them to existing standards of care as applicable. This scientific inquiry prompts researchers to design and develop proposed clinical trial protocols to evaluate preliminary information about the product and develop research questions and objectives. The average budget for new product development is enormous, and this eventuality is because almost 90 percent of a trial drugs never get approved. Hence, having an appropriate clinical trial design is crucial for successful product development. A trial's ability to deliver the proposed indication relies on its suitable design, background information, the trial justification to sample size, interim monitoring rules, and ways to review and analyze study data. In this article, we presented an overview of clinical trial designs emphasizing adaptive designs in a simplified way for field-based clinical research professionals.

Keywords: Clinical trial design, Adaptive clinical trial design, Types of clinical trial, Randomized control clinical trial, Placebo control clinical trial

INTRODUCTION

The objective of the clinical trial is to assess the safety, efficacy, and risk-benefit ratio of the investigational product so that its superiority, non-inferiority, or equivalence can be evaluated. The clinical trial design is the crucial element of interventional trials that boosts ergonomics and economizes clinical trial conduct.

Protecting the study participants is paramount while designing clinical trials.[1] Clinical trials are inspected by entities overseeing the research studies, such as institutional review boards, Food and Drug Administration (FDA), health authorities, data, and safety monitoring committees. FDA governs clinical trial conduct while ensuring that clinical trials are designed, conducted, analyzed, and reported according to the 21 CFR code of federal regulations, following suggested ICH-GCP guidelines and producing the robust quality clinical evidence needed to assess product safety and efficacy. In 2022, FDA launched the complex innovative trial design paired meeting program to enhance the use of convoluted novel, adaptive, and Bayesian clinical trial designs in product development.

TYPES OF CLINICAL TRIALS

Uncontrolled trials

As the name suggests, this trial design contains a no-control arm. To assess the pharmacokinetic properties of a new product, this design is accommodated in the phase 1 trial. Due to the possibility of integral bias, this design produces study results that are less acceptable than randomized control trials.[2]

Controlled trials

Marketing new drugs or biologics requires the study sponsor to demonstrate product safety and efficacy

through adequate and well-controlled clinical studies. This design compares study participants who receive new investigational products to participants who receive suitable control products. There are five different types of control for various scenarios: no-treatment concurrent control, historical control, dose-comparison concurrent control, placebo concurrent control, and active-treatment concurrent control.[1]

Controlled trials distinguish patient outcomes from others using various outcomes-causing factors such as patient or observer expectation and natural history. Hence, correct control, correct dose, and selection frequency are crucial for the trial's success.[2]

No treatment concurrent control

As the name suggests, no intervention is administered in the control arm in this design; when objective evidence of effectiveness exists, and the placebo effect is insignificant, the investigational product is compared with no treatment. This design usually includes randomization.

Active, treatment, concurrent control

This design compares a new therapy with the approved therapy or the combination of new and approved therapies with the standard therapy alone. It also ascertains the study intervention's equivalence, non-inferiority, and superiority. Per the Declaration of Helsinki, the standard treatment should be used as the control group; therefore, this design is considered the most ideal.

Dose-comparison, concurrent control

In this design, active and control arms consist of different doses or schemas of the study treatments. The goal is to determine the relationship between the intervention's dose, efficacy, and safety.

Historical control

Owing to the difficulty in ensuring the comparability of historical control groups to the group of treated subjects about the variables that could impact the outcome, the regulation noted to use of historical control studies for unique circumstances, such as when the effect of the drug is noticeable, the disease with high and explicit mortality.[1]

Placebo control

This design is used to ascertain superiority or equality and is used only when existing effectual approved treatments are unavailable. Using a placebo is considered unethical if a sufficient standard of care option is available.

Placebo is acceptable if no irreversible harm occurs due to the delayed administration of available treatments, with acceptable minimal risk and for short-duration trials.[3]

Another variant of placebo-controlled trial designs

Placebo, run-in design

In this design, a placebo is administered to all study subjects in the run-in period before the clinical trial begins. It not only provides baseline findings but also screens unsuitable participants, and only stable eligible participants get randomized into active and placebo arms.

An unbalanced assignation of participants to placebo and test treatment

In this design, fewer patients were randomized to the placebo group than the investigational product group.

Double-dummy design

This design is instrumental if the comparing investigational product arms are of different natures, for example: investigational drug group, = investigational product+ placebo, active control group = placebo + active control group.

Add-on design

This design shows a placebo-controlled comparison in addition to the standard treatment given to all participants. Such a trial may be extensive if the observed improvement due to added features is slight as compared to the standard treatment.

Early escape design

This design shortens the time subject is exposed to placebo or treatment failure as it allows early patient removal from the study on the establishment of predefined, lower efficiency.

RANDOMIZED CLINICAL TRIALS

Randomized clinical trials (RCT) is also called parallel group randomized trials or randomized controlled trials. It includes the randomization of eligible study participants with two or multiple arms. One of the arms receives experimental therapy; the other receives the placebo and standard-of-care therapy. Randomization is conducted by a computer system provided by the study sponsor called as "IWRS or "IRT- intra voice reporting system" so that outcomes and the effectiveness of study interventions can be studied without bias.

Randomization, methods

Stratified randomization

Stratified randomization aims to ensure the treatment groups' balance with the prognostic variables' various patterns. The number of stratifications must be minimal to get good results.[4]

Example of stratification

Block randomization – a commonly used technique to reduce bias and set up the treatment balance, specifically when the sample size is small. Sequencing individual participant assignments by block escalates the possibility of the same number of participants in each arm. For example, the blocking factor could be the sex of a participant; the blocking factor sets up the evenness leading to greater accuracy.[5]

Given or paired organs (split body trials)

As the name suggests, in this type of stratification, one Investigational product is dispensed to one side of the body, and the comparison group investigational product is dispensed to another half side of the body. This design is often used in locally acting interventional dermatology and ophthalmic clinical trials. The randomization method is used to assign intervention. The benefit of this method is that it removes the confusing factors among interventional study arms. In contrast, the disadvantages are, administering an investigational product on one part of the body can influence its effect on another, demanding blind statistical analysis and obscuring systemic adverse events.[6]

Cluster randomization

Cluster-randomized trials (CRT) are frequently used to compare interventions assigned to entire groups of subjects rather than individuals. The groups of participants form a cluster and serve as the unit of randomization. Each cluster receives either active or comparator intervention. This design can be implemented in clinical practices, schools, hospital/ICU wards, or regional geographic areas. It is specifically suited for implementation studies like population lifestyle interventions, treatment guideline outcomes, and community vaccinations.[7]

Allocation by randomized consent (Zalen trials)

To facilitate the clinicians' and patients' participation Marvin Zelen advised a new design that includes the random assignment of the treatment arm before the participant consented. After the randomization, the participant would receive assigned treatment information and be approached to consent. This design requires a waiver of the informed consent before any study-related procedures are performed; hence it cultivates intense ethical concern and must only be used in clinical trials with great public health importance and deficient study population.[8]

Minimization

This dynamic randomization lowers the imbalance between treatment groups and can be considered platinum standard randomization.[9]

RANDOMIZED CONTROL, CLINICAL TRIAL DESIGNS

Parallel group, trial design

This clinical trial design is included in most therapeutic area clinical trials. Each study arm is a different intervention, and participants are enrolled into one or more treatment arms; an example of treatment arms are specific doses of the study drug, a placebo, or a standard of care treatment. After randomization, patients will remain in the same treatment arm throughout the trial. This design can be helpful in many diseases and in several groups located in individual locations. The disadvantage of this design is that participants may prefer to avoid being randomized to the placebo arm, which could be a repealing factor for participants not participating in the clinical trial.

Cross-over design

Crossover study design is another way to compare groups in the research study, and it usually requires fewer patients than the parallel-group study. Each patient behaves as his or her control and is subsequently randomized into study arms, study drug arms, placebo arms, or standard-of-care treatment arms. Randomization decides the series of interventions. The duration of cross-over studies is long as it includes the random assignment of study subjects to one arm, which then crossovers with another treatment arm during the trial. Owing to the longer duration of the study, this design risks dropping a significant number of patients before the study completion, which leads to compromised study data. For ensuring data integrity, a washout period is often used, during which patients receive no treatment, so carryover effects from the earlier intervention get reduced. The outcomes of the various arms are then compared within the same subject. This design requires diseases that are chronic, stable, and incurable, and the effect of each intervention should be reversible, for example, bioequivalence, and biosimilar equivalence protocols with crossover design.[9,10]

Variations of crossover designs

Switchback design (A arm-B arm-A arm versus B arm-A arm-B arm)

The introduction of biosimilars emerged the switchback and multiple switchback designs.

N of 1, design

This eventuality is also called a "single-subject" trial, which consists of several random, repeated experimental control treatments for the individual patient with the primary objective of determining the treatment preference for the patient. The advantage of this design is flexibility and ongoing continuation of the trial until the confirmed conclusion is drawn for the subject being studied. The advantage depends on the analyzing treatments, which

produce heterogeneous effects in various subjects; data from various subjects can also be merged with meta-analysis or Bayesian methods to derive population effect sizes.

Factorial design (2×2 design)

This design helps understand the impact of two independent factors, each with two levels on a single dependent variable. For example, a randomized trial testing aspirin versus placebo and clonidine versus placebo. In this case, each patient will either receive clonidine or placebo and aspirin or placebo. The chief effect of aspirin and clonidine can be measured using a two-way variance analysis ANOVA. Clinical trials with this design can provide answers to two or more research questions while achieving more restricted sample sizes. However, the limitations of this trial design are the complexities from various perspectives, such as protocol conduct, statistical analysis of the trial, and the inability to combine two incompatible interventions.[11]

Adaptive design

Potential, advantages, and examples

The adaptive design permits the trial to adjust to the new information that didn't exist initially, providing various advantages over non-adaptive designs. The design could allow early discontinuation if it showed no efficacy, stopping further exposure of study participants to ineffective study treatment and allowing subjects to try better therapeutic options. The design can provide better results with a smaller required sample size or shorter required duration as compared to a non-adaptive design.[12] Fixed adaptive design answers broader questions and provides an improved understanding of the effect of the investigational product. Sponsors should commit to a design that permits planned design modifications based on interim data analysis.[13]

Adaptive design based on non-comparative data

In this design, the adaptations are centered solely on the analyses of non-comparative data without including treatment assignment information. Hence, it is sometimes called blinded or masked analyses. Study data have no or a small effect on the Type I error chance, making this design appealing, especially considering the high uncertainty about event probabilities or endpoint variability.[14]

Adaptive design based on comparative data

Contrasted to non-comparative adaptation design, comparative adaptation frequently increases the type I error possibility and stimulates bias in treatment effect evaluations. Hence, statistical methods and additional steps are added to ensure appropriate trial conduct in this design. This design includes following different subtypes of designs with predetermined rules for halting the trial or transforming the design based on interim analyses of comparative data.[15]

Group, sequential designs

Sequential analyses are beneficial from an ethical and efficient perspective by lowering the expected sample size and duration of clinical trials and facilitating regulatory approval. Without sufficient proof of efficacy for regulatory approval, this design also includes rules for stopping the trial. This design is successful with prolonged study enrollment and in cases of early treatment outcomes, so the outcomes can be analyzed before more patients are recruited. Some of the challenges of this design are the intricacy of analyzing multiple treatments and a fair number of interim analyses, along with their timing.[16]

Adaptations to the sample size

This design includes a potential plan for modifying the sample size based on interim analysis results using treatment assignment information. In another adaptive approach, unblinded sample size adoption or unblinded sample size re-estimation, there is a potential plan for modifying the sample size based on comparable interim results.[17]

Adaptations to the patient population

This design permit modification to the patient population based on comparable interim results. Often, the treatment effect could be more significant on a specific trial population based on certain factors, such as certain genetic and demographic factors that could affect the impact of the study drug. In such a scenario, after interim analysis, a decision will be taken based on predetermined conditions whether to continue the recruitment of general participants or to restrict further recruitment to the focused patients.[18]

This design is called an adaptive enrichment design, which is more beneficial than non-adaptive designs.[19] In contrast to the focused subpopulation-controlled trial, this design permits an assessment of the study intervention in the non-focused subpopulation.

Adaptations to treatment arm, selection

This design includes a prospective plan for modifying the trial intervention depending on comparative interim results. Modifications may include enhancing or reducing arms. This design is frequently used for early-phase exploratory dose-ranging trials, which could start with several doses. Comparative data is analyzed after interim analyses to select doses for further continuation to provide an improved picture of the dose-response relationship compared to the non-adaptive design, with the best dose or doses for future confirmatory investigations. Seamless designs that include dose selection and validation of the

efficacy of selected doses can be considered if the principles for adaptive designs are implemented.[20]

Adaptations to patient allocation

There are two types of adaptations to patient allocation.

Comparative baseline characteristic data-based adaptations known as covariate-adaptive treatment assignment. In this design patient's treatment assignment relies completely or partly on; the patient's baseline features and the baseline features and study arm of the earlier enrolled patients.

Comparative outcome data-based adaptations are known as response-adaptive randomization. The possibility of a newly enrolled subject being randomized to a treatment arm varies over the duration of the trial, and it relies on the gathered outcome data of earlier enrolled participant's subjects. This design works best in outcome trials with a relatively short duration. Play, the winner design is one of the varieties of response-adaptive randomization techniques.

Adaptations to endpoint selection

This design permits adaptive modifications to the choice of primary endpoint established on the comparative interim results. The design might be influenced by uncertainty about the treatment effect sizes on many patient outcomes; hence, while considering this design, consultation with the FDA review division is suggested as endpoint selection includes critical clinical considerations.

Adaptations to multiple design features

Combining two or more adaptive design concepts can make the clinical trial design more complex; however, the general principles remain the same as simpler adaptive designs.

Restrictions of adaptive design

The restriction of adaptive design is the longer time interval between planning and starting the trial, as the pre-planning efforts require more effort. Furthermore, although the design reduces the minimum and required sample size, it could also increase the maximum size compared to a non-adaptive design.[21]

The design faces logistical challenges to ensure trial integrity and trial conduct, and demanding scientific restrictions limits the opportunity for adaptive efficiency. Adaptive designs require specific analytical methods and the critically required simulation to avoid erroneous bias and results.

However, these features are only sometimes available for complex adaptive designs.[13]

CONCLUSION

While innovations in the computing and statistical sphere are beneficial to accommodate increasingly multifaceted study designs, they also have challenges and concerns. In addition, many factors can play an essential role in selecting the best suitable clinical trial design, such as study duration, study population and their required number, study logistics, study objectives, study time, and how the variability is handled. Unfortunately, no confirmed, well-established, perfect trial design can provide us with the best answers for all our research-related questions. To make clinical trials faster, less costly, and more successful, many pharmaceuticals are utilizing adaptive trial designs as their default design due to the fundamental advantage of this design over non-adaptive design. We conclude that there is no fixed definition of the best clinical trial design, which can be considered the best innovative design, as the expectation requirement, the design tools with new ideas and advanced added features can change over time according to the need. Hence, while considering study objectives, questions, and other study requirement researcher will need to research, select, modify and develop the best trial design, probably with several specialized features to make successful, faster, less costly, and more efficient clinical trials.

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REFERENCES

1. Office of the Commissioner & Office of the Commissioner. 2018. Drug Study Designs. U.S. Food and Drug Administration. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-study-designs. Accessed on 09 March 2023.
2. Nair B. Clinical Trial Designs. Indian Dermatol Online J. 2019;10(2):193.
3. Enck P, Klosterhalfen S. Placebos and the Placebo Effect in Drug Trials. Handbook Exp Pharmacol. 2019;399-431.
4. Chidambaram AG, Josephson MB. Clinical research study designs: The essentials. Pediatric Investig. 2019;3(4):245-52.
5. Efird JT. Blocked Randomization with Randomly Selected Block Sizes. Int J Env Res Public Health. 2010;8(1):15-20.
6. Higgins JPT, Eldridge S, Li T. Chapter 23: Including variants on randomized trials. Cochrane Handbook

for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane. 2022.
7. Jaikumar V. Cluster Randomized Trials: Concepts - Tutorials and Fundamentals. Students 4 Best Evidence. 2022.
8. Simon GE, Shortreed SM, DeBar L. Zelen design clinical trials: why, when, and how. Trials. 2021;22(1).
9. Jin M, Polis AB, Hartzel J. Algorithms for minimization randomization and the implementation with an R package. Communications in Statistics - Simulation and Computation. 2021;50(10).
10. Turner JJ. Crossover Design. Springer eBooks. 2013;521.
11. Krzywinski M, Altman N. Two-factor designs. Nature Methods. 2014;11(12):1187-8.
12. Chen Y, Gesser RM, Luxembourg A. A seamless Phase IIB/III adaptive outcome trial: Design rationale and implementation challenges. Clinical Trials. 2015;12(1):84-90.
13. Center for Drug Evaluation and Research. Adaptive designs for clinical trials of drugs and Biologics guidance. U.S. Food and Drug Administration. 2019. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry. Accessed on 09 March 2023.
14. Dodd LE, Proschan MA, Neuhaus J, Koopmeiners JS, Neaton JD, Beigel JH, et al. Design of a Randomized Controlled Trial for Ebola Virus Disease Medical Countermeasures: PREVAIL II, the Ebola MCM Study. J Infect Dis. 2016;213(12):1906-13.
15. FDA-NIH Biomarker Working Group. Best (biomarkers, endpoints, and other tools) resource. National Center for Biotechnology Information. 2016.
16. Fisher LD. Self-designing clinical trials. Statistics Medicine. 1998;17(14):1551-62.
17. Friede T, Kieser M. Blinded sample size reassessment in non-inferiority and equivalence trials. Statistics in Medicine. 2003;22(6):995-1007.
18. Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine. 2010;29(2):219-28.
19. Gould A. Sample size re-estimation without unblinding for normally distributed outcomes with unknown variance. 1992. Available at: https://www.semanticscholar.org/paper/Sample-size-re-estimation-without-unblinding-for-Gould-Shih/219e5dc9baa20fc879c6629cbf5925111fc5df4. Accessed on 09 March 2023.
20. Stallard N, Todd S. Seamless phase II/III designs. Statistical Methods in Medical Research. 2011;20(6):623-34.
21. Cui L, Hung HMJ, Wang S. Modification of Sample Size in Group Sequential Clinical Trials. Biometrics. 1999;55(3):853-7.

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