

Principles of Good Clinical Trial Design



Ming-Wen An, PhD,^{a,*} Quyen Duong, PhD,^b Jennifer Le-Rademacher, PhD,^b
Sumithra J. Mandrekar, PhD^b

^aDepartment of Mathematics and Statistics, Vassar College, Poughkeepsie, New York

^bDepartment of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

Received 14 February 2020; revised 13 April 2020; accepted 4 May 2020

Available online - 15 May 2020

ABSTRACT

Clinical trials are a fundamental component of medical research and serve as the main route to obtain evidence of the safety and efficacy of treatment before its approval. A trial's ability to provide the intended evidence hinges on appropriate design, background knowledge, trial rationale to sample size, and interim monitoring rules. In this article, we present some general design principles for investigators and their research teams to consider when planning to conduct a trial.

© 2020 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

Keywords: Principles; Clinical trial; Design; Collaboration

Introduction

Clinical trials are a fundamental component of medical research. Before any treatment is approved and offered to patients in the general population, rigorous evidence of its safety and efficacy must be reported. Clinical trials are the main route to obtain this required evidence. In this article, we present some general principles of good clinical trial design, which are often used as the basis to evaluate the quality of the evidence presented in manuscripts reporting trial results. By trial design, we include aspects from background knowledge and trial rationale to sample size and interim monitoring rules. Given that mistakes in design can only be rarely rectified, we strongly encourage investigators to consider these guidelines before beginning a study.

The critical component for a successful design is the relationship between the different members of the scientific team. This is important because each person on the team contributes in their area of expertise to come up with a feasible study that meets the scientific hypothesis. It is crucial to involve statisticians in the very early stages of the study design instead of waiting to

involve them at the time of data analysis. Not only can statisticians help with assessing the design parameters and calculating the sample size needed to address the study aims, but they also ensure that the statistical hypotheses appropriately align with the study objectives and that the corresponding statistical analyses are correctly applied. Note that it is very difficult to fix a poorly-designed study once it is implemented.

The design process of a clinical trial is iterative in nature with some of the steps being inherently connected to others, but it can be helpful to divide the process into two phases, namely: conceptual planning and implementation (Fig. 1). The conceptual planning phase includes establishing previous knowledge and background, thinking through the rationale for the proposed trial as it relates to the patient population and the intervention under consideration, considering the outcomes of interest and statistical design parameters, including stratification factors, and determining the trial phase. The implementation phase is the part in which the design parameters necessary to run the trial are specified and consists of performing sample size calculations, defining interim monitoring and stopping rules, and conducting simulation studies to evaluate the operating characteristics of the proposed design. In the remainder of this article, we frame our guidelines around these phases of the design process of a clinical trial. Throughout the article, we provide references for the

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Ming-Wen An, PhD, Department of Mathematics and Statistics, Vassar College, 124 Raymond Avenue, Poughkeepsie, NY 12604. E-mail: mian@vassar.edu

© 2020 International Association for the Study of Lung Cancer. Published by Elsevier Inc. All rights reserved.

ISSN: 1556-0864

<https://doi.org/10.1016/j.jtho.2020.05.005>

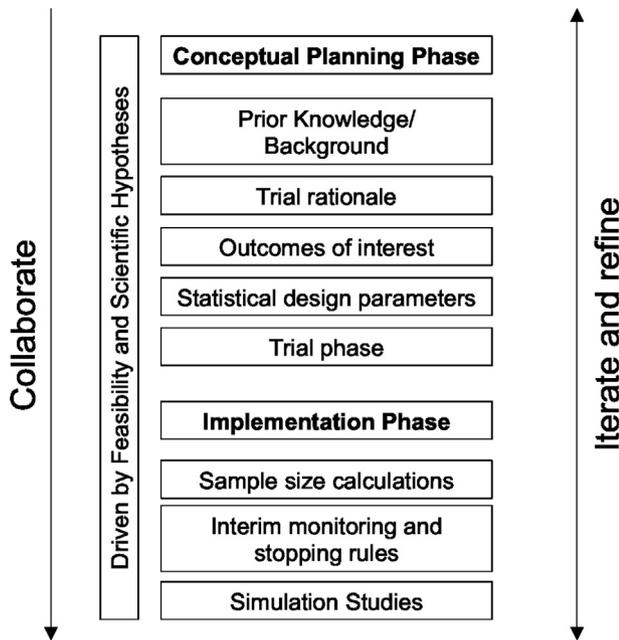


Figure 1. Principles for conceptual planning and implementation stages.

interested reader to find further details and explanations of concepts and terms.

Conceptual Phase

In this section, we outline the different areas that need careful attention when considering a clinical trial.

Previous Knowledge and Background

The first step in designing a clinical trial is to establish what is known about the disease being studied. Specifically, this includes identifying the current standard of care and reviewing what is already known about the intervention(s) being studied, including its safety profile and whether it has been tested in humans.

Trial Rationale

It is important to justify the need for the proposed trial, to identify the population of interest, and to determine the disease or biomarker prevalence in this population. When the disease is rare or a targeted subgroup is of interest, then specific study designs for these settings may need to be considered.¹⁻³ Similarly, there is extensive work in the literature on study designs for personalized medicine in oncology.⁴

Outcomes of Interest

Once the rationale for a trial has been established, the selection of the outcome(s) of interest is essential. Trial outcomes can be either health- or treatment-related.

Examples of health outcomes include quality of life, symptoms, adverse events, and patient-reported outcomes. Treatment outcomes include assessing the safety or efficacy of the intervention; examples include tumor shrinkage, hematologic outcomes, intermediate, or surrogate outcomes, time-to-event outcomes (e.g., overall survival or progression-free survival), and surgical outcomes. It is common to have one or two primary outcomes and one or two secondary outcomes. The primary outcome should be directly related to the mechanism of action of the intervention, clinically meaningful, relevant to the patient, clearly defined, and measurable. These principles that highlight the importance of the design process are collaborative, not only among clinicians and statisticians, but also among patients, patient advocates, and their caregivers. Friedman et al.⁵ and Wu and Sargent⁶ offer more considerations for choosing end points.

Statistical Design

Estimating treatment effect is a common goal of many studies. Single-arm designs—in which all patients receive the same intervention and are generally compared with a historical control group—can provide some information on treatment effect. However, oftentimes, the single-arm group of patients and the historical control group neither represent the same populations of interest nor receive treatment under similar trial conditions. As such, single-arm designs are limited in the conclusions they can draw and less desirable than randomized trials. In randomized trials, there are at least two treatment groups (or “arms”) to which patients are randomly assigned. The random assignment, or randomization, aims to create groups that are similar with respect to all factors, besides the intervention, that might affect the outcome. This is a key principle of randomized trials that ensures a fair comparison. Randomized trials can likewise incorporate other design components. Common examples include the use of a control arm (i.e., an arm that receives the standard of care) and blinding (i.e., patient and/or clinician do not know the treatment assignment) to reduce bias. Randomization can be balanced, i.e., both groups are of equal size or unbalanced, i.e., the groups are of unequal size. Finally, when confounding factors may be of concern, stratification may be considered as an additional design component. Although randomization aims to reduce confounding by making the treatment groups as similar as possible except for the treatment assigned, it is, nevertheless, possible for the groups to differ with respect to some important factors (i.e., imbalance). Examples of such factors include sex, age, and other factors specific to the study context. Stratification entails grouping patients into strata according to these

important factors and then randomizing within each stratum. Identification of such potential confounding factors and including stratification as part of the randomization process can minimize the potential for imbalance. In addition, there are also specific considerations with regard to several other study designs, including adaptive, group sequential, and Bayesian designs,⁷⁻¹¹ and when drafting a statistical analysis plan for clinical trials.¹²

Trial Phase

The traditional development of new therapeutic interventions occurs in phases of trials, from preclinical to postmarket; and so, one must consider the available information about the intervention and the targeted population (among others) to better understand the trial phase for the study under consideration. Early phases of clinical studies include pilot studies, phase I, phase II single-arm, and proof of concept. Later phases of clinical studies include randomized phase II, phase II-III, and phase III trials. Phase II trials aim to further understand the safety and efficacy of an intervention to help decide whether or not to proceed to a phase III trial. Phase II and phase III trials typically have different end points; phase II trials utilize short-term, early end points such as response rate or event-free survival rate at a pre-determined time point whereas phase III trials utilize long-term clinical outcomes such as overall survival.¹³ Given the role of phase II trials in determining the go/no-go decision to proceed for further testing in large confirmatory phase III trials, it is crucial to select an appropriate end point, particularly in phase II trials. Phase II end points should ideally be strong surrogates for the phase III end points.¹⁴

Implementation Stage

Once the design elements in the conceptual phase have been identified and there is consensus to move forward with designing a clinical trial, the design elements necessary for the actual running of the trial need to be specified. This constitutes the implementation phase, the steps for which are outlined below.

Sample Size Calculation

The purpose of sample size calculation is to determine the number of patients needed to be enrolled in the study to provide sufficient information to address the primary objectives. For traditional randomized designs, this depends on three primary factors that the research team must decide together—effect size, (statistical) power, and statistical significance level. Effect size refers to the minimum treatment effect that one hopes to detect in the study. Power refers to the likelihood of detecting an

effect when in fact there is an effect of a previously specified size. Significance level refers to the p value threshold for concluding statistically significant results; it also corresponds to the type I error rate (the chance of concluding an effect exists when in fact none exists). In general, larger sample sizes are needed to detect a smaller effect size, achieve greater power, and/or reduce the type I error rate. In addition to these factors, sample size calculations for trials should anticipate loss to follow-up and withdrawals, patient noncompliance to treatment, and protocol violations and ineligibility. Sample size calculations should be adjusted (specifically, increased) on the basis of expected rates of these various sources of patient “drop-out.” Finally, examining the population of interest will help determine the expected accrual rate, and in turn, the expected time to accrue the total required number of patients to the trial. Sample size considerations for Bayesian designs depend on additional factors, most notably the previous distribution of the effect size.¹⁵

Interim Monitoring and Stopping Rule

Clinical trial monitoring is critical to the conduct—especially the ethical conduct—of the trial, and as part of this, it is important to decide the number and timing of interim analyses to be conducted before the completion of data collection and build this as part of the design. Furthermore, it is important to specify parameters for all stopping rules for stopping the trial early. In a Frequentist design, stopping rules are defined in terms of boundaries for safety, efficacy, and futility.¹⁶ In a Bayesian design, stopping rules are typically defined in terms of posterior probabilities or predictive probabilities.¹⁷

Simulation Studies

Finally, even with the best trial design, actual trials seldom go as planned as unanticipated scenarios may arise. Therefore, while designing the trial, it is helpful to brainstorm these unanticipated scenarios as much as possible, and understand their implications using simulation studies. Simulation studies, when designed well with realistic scenarios, are a valuable tool for evaluating different trial designs and scenarios without exposing patients to ineffective or harmful therapy or incurring the high financial costs associated with running an actual trial. The insights gained from simulation studies can help further guide the design process.

Conclusion

The goal of this article is to provide initial guidance to investigators through the design process of a clinical trial. It is not meant to be a strict set of rules to be

followed in some prescribed order; rather, it is meant to be a set of guidelines to be considered in active collaboration with the study team, including a statistician. These principles should apply to the design of any clinical trial, regardless of who initiates and conducts the study (e.g., research group versus industry). The importance of involvement of the statistician throughout the entire research cannot be overemphasized. The statistician can aid in each step, from formulating appropriate scientific hypotheses to designing and conducting simulation studies. In addition to being collaborative, the design process is also iterative; it may be that some design elements need to be modified after other design elements are considered. For example, the trial phase is typically driven by the level of available evidence on the drug being tested. However, occasionally, the choice of trial phase (e.g., phase II versus phase III) may be driven by feasibility to launch a large trial. Ultimately the design must be feasible and appropriate to answer the research question(s) of interest.

This article is also not meant to provide an extensive review of design principles; for that, we refer the interested reader to the references included in this article that offer detailed guidelines for designing trials. Furthermore, two reports on statistical design, including the Statistical Principles for Clinical Trials¹⁸ and Guideline for Good Clinical Practice,¹⁹ have been drafted by the International Council on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use in 1998 and 2016, respectively. The frequently cited reference by Altman et al.²⁰ also outlines statistical guidelines for preparing a manuscript for medical journals.

Expanding these principles for novel study designs, including immunotherapy and cellular therapy trials, and also cancer care delivery research that spans multiple disciplines (in which randomization must be made at the patient, provider, and site levels) could be considered in future work.

Acknowledgments

This work is funded in part by 5K12CA090628 and P30CA15083 (Mayo Clinic Comprehensive Cancer Center Grant).

References

1. Le-Rademacher J, Dahlberg S, Lee JJ, Adjei AA, Mandrekar SJ. Biomarker clinical trials in lung cancer: design, logistics, challenges, and practical considerations. *J Thorac Oncol*. 2018;13:1625-1637.
2. Gupta S, Faughnan ME, Tomlinson GA, Bayoumi AM. A framework for applying unfamiliar trial designs in studies of rare diseases. *J Clin Epidemiol*. 2011;64:1085-1094.
3. Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. *J Clin Oncol*. 2009;27:4027-4034.
4. Renfro LA, Mandrekar SJ. Definitions and statistical properties of master protocols for personalized medicine in oncology. *J Biopharm Stat*. 2018;28:217-229.
5. Friedman LM, Furberg CD, DeMets D. *Fundamentals of Clinical Trials*. 4th ed. New York, NY: Springer-Verlag; 2010.
6. Wu W, Sargent D. Choice of Endpoints in Cancer Clinical Trials. In: Kelly WMK, Halabi S, eds. *Oncology Clinical Trials: Successful Design, Conduct, and Analysis*. New York, NY: Demos Medical Publishing; 2010.
7. Pallmann P, Bedding AW, Choodari-Oskooei B, et al. Adaptive designs in clinical trials: why use them, and how to run and report them. *BMC Med*. 2018;16:29.
8. Bhatt DL, Mehta CM. Adaptive designs for clinical trials. *N Engl J Med*. 2016;375:65-74.
9. Vandemeulebroecke M. Group sequential and adaptive designs - a review of basic concepts and points of discussion. *Biometrical J*. 2008;4:541-557.
10. Lee JJ, Chu CT. Bayesian clinical trials in action. *Stat Med*. 2012;31:2955-2972.
11. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5:27-36.
12. Gamble C, Krishan A, Stocken D, et al. Guidelines for the content of statistical analysis plans. *JAMA*. 2017;2337-2343.
13. Foster JC, Le-Rademacher J, Mandrekar SJ. Design considerations for phase II. In: Roychoudhury S, Lahiri S, eds. *Statistical Approaches in Oncology Clinical Development*. 1st ed. New York, NY: Taylor and Francis Group; 2018.
14. Yin J, Dahlberg SE, Mandrekar SJ. Evaluation of end points in cancer clinical trials. *J Thorac Oncol*. 2018;13:745-757.
15. Pezeshk H. Bayesian techniques for sample size determination in clinical trials: a short review. *Stat Methods Med Res*. 2003;12:489-504.
16. Ellenberg SS, Fleming TR, DeMets DL. *Data Monitoring Committees in Clinical Trials: A Practical Perspective*. Chichester, England: John Wiley & Sons; 2002.
17. Saville BR, Connor JT, Ayers GD, Alvarez J. The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. *Clin Trials*. 2014;11:485-493.
18. European Medicines Agency. ICH topic E 9 statistical principles for clinical trials. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf; 1998. Accessed March 12, 2020.
19. European Medicines Agency. Guideline for Good Clinical Practice E6(R2). https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf; 2016. Accessed March 12, 2020.
20. Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *Br Med J*. 1983;286:1489-1493.