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A Note of Adaptive Design in Clinical Trials

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Abstract

During the past decades, adaptive design in clinical trials has gained more and more attention in the industry and academia, not only for early phase/exploratory trials but also for confirmatory trials. Adaptive design is also endorsed by the regulatory agencies, if performed with care [1-2]. This paper provides an overview of the basic concepts of adaptive design in clinical trials, including the adaptation rules, types of adaptive design, and statistical principles of data analysis as well as the Type I error control. Operational hurdles and regulatory challenges are discussed as well.

Keywords: Adaptive design; Interim analysis; Group sequential; Adaptation rule; Sample size re-estimation

Abbreviations: FDA: Food and Drug Administration; EMA: European Medicines Agency

Introduction

During the past decades, the potential use of adaptive designs in clinical trials has gained more and more attention, not only for early phase/exploratory trials but also for confirmatory trials. Adaptive designs are also endorsed by the regulatory agencies, if performed with care [1-2]. The concept of adaptive designs initially came under the Critical Path Initiative by the US Food and Drug Administration (FDA) in 2004, which aimed to encourage sponsors to innovate and speed up the drug development process, and attempted to offer flexibility for sponsors to find the optimal clinical benefit without affecting the study's integrity and validity. FDA has released more than one guidance document on the subject of adaptive design since 2010, e.g., the draft guidance on adaptive design clinical trials for drugs and biologics [2] and the final guidance on adaptive design for medical device clinical studies [3]. The European Medicines Agency (EMA) also released an official guiding document on adaptive clinical trial [1]. These guidance documents cover a wide-range of aspects about adaptive design including clinical, statistical, and regulatory, and provide valuable insights to the clinical research in the industry and academia.

This article is aimed to review the basic concepts of adaptive designs in clinical trials, including the adaptation rules, types of adaptive design, and statistical principles of data analysis as well as the Type I error control. The current regulatory perspectives and operational hurdles are discussed as well.

Basic concepts of adaptive design

Classical drug development consists of a sequence of independent trials. Adaptive design aims at interweaving these trials by combining them into one single study conducted in two or more stages [4-5]. Adaptive design uses the accumulating data to decide on how to modify the aspects of a study without undermining the validity and integrity of the trial. To maintain the study validity, correct statistical methodology should be utilized to allow the modification of the design element at an interim analysis with full control of the Type I error [1], assure consistency between different stages of the study, and minimize the operational bias. To maintain the study integrity, the study should be properly executed following the prespecified adaptation rules and maintaining the blind of interim analysis results.

As compared to other designs, adaptive design is considered to have the potential to improve the performance of the clinical trials by enhancing the flexibility and efficiency of drug development via allocating resources more efficiently, reducing the decision-making time and saving cost through the combination of evidence across studies without lowering regulatory standards.

Development of adaptive design

Wald [6] pioneered sequential analysis in 1947. Armitage [7,8] first adopted it to the field of clinical trials. Pocock [9] and O'Brien & Fleming [10] introduced the group sequential test, which was considered more practical than the pure sequential test. Lan & DeMets [11] proposed a more flexible approach with the alpha-spending function. On the basis of sequential analysis and group sequential analysis, adaptive design was initiated by Bauer [12], who demonstrated the adaptive design was superior compared to the classic group sequential designs as adaptive design provided the potential for substantial data-driven re-design [13], e.g., modification of adaptive randomization to achieve balance within

strata, sample size re-estimation, early stopping due to efficacy or futility, dropping inferior treatment groups, and change of treatments, patient population, hypotheses or the order of hypotheses.

Adaptation rules

The real merit of adaptive design is adaptations going beyond the traditional sample size re-estimation. In general, the adaptation rules include but not limited to:

I. Randomization rules. It is desirable to randomize more patients to superior treatment groups, which can be achieved by increasing the probability of assigning a patient to the treatment group when the evidence of responsive rate increases in a group [14-15].

II. Early stopping rules. It is desirable to stop trial when the efficacy or futility of the test drug becomes obvious during the clinical trial.

III. Dropping loser rules. One can improve the efficiency of a trial by dropping some inferior treatment groups during the clinical trial.

IV. Sample size re-estimation rules. It is desirable to adjust the sample size according to the effect size of an ongoing clinical trial.

Types of adaptive design

Based on the level of flexibility, adaptive design can be categorized into three classes: rigid, totally flexible, or partially flexible.

i. Rigid Adaptive Designs. The scope of possible adaptations and decisions are pre-specified up front in the protocol [16].

The advantages of rigid adaptive designs include that logistical problems such as changing treatments, patient eligibility, and accrual rates can be planned for in advance; there is no need to file protocol amendments; final analysis can be conducted based on sufficient statistics; sample size can be statistically justified, etc. However, rigid adaptive designs are not able to respond to unexpected circumstances during a long-term trial, and information about progress of the trial is more easily inferred.

ii. Totally Flexible Adaptive Designs. Unplanned design modifications can be made at unplanned interim analyses, which is also called "Self-designing trials" [17].

The advantage of totally flexible adaptive designs is the ultimate flexibility. However, the ad hoc design modifications based on unblinded interim results can lead to loss of credibility, and it requires the use of unfamiliar test statistics which can be a source of inefficiency [18-19], and can lead to possible anomalous results [20]. Also, the point and interval estimation may be problematic.

iii. Partially Flexible Adaptive Designs. Partially flexible adaptive design is a compromise. For example, the design and length of Stage 1 are fixed in advance.

The design of Stage 2 is permitted to depend on Stage 1 results in an arbitrary and unplanned way. Final inference must be based on the p-values from the two stages according to a rule specified in advance. By applying the method recursively, multistage designs can be constructed.

Based on the adaptations employed, adaptive design can be categorized into but not limited to the following [21]:

1) Adaptive randomization design: An adaptive randomization design allows modification of randomization schedules based on varied probabilities of treatment assignment to increase the probability of success. Although an adaptive randomization design could increase the probability of success, it may not be feasible for a large trial or a trial with a relatively long treatment duration because the randomization of a given subject depends on the response of the previous subject.

2) Group sequential design: A group sequential design allows for prematurely stopping a trial due to safety, futility, or efficacy based on the interim analysis results. The stopping boundaries are obtained based on different boundary functions with the control of Type I error [14-15,22-24]. The concept of two-stage adaptive design has led to the development of the adaptive group sequential design [25-28].

3) Sample size re-estimation design: A sample size re-estimation design allows for sample size adjustment or re-estimation based on the interim analysis results, e.g., promising zone design [29]. It is worth noting that the observed treatment difference at the interim based on a small number of subjects may not be statistically significant. In addition, the knowledge of sample size adaptation rules may lead to potential unblinding by allowing the back-calculation of the interim treatment effect from the adaptively chosen sample size. Thus, caution should be taken to maintain the blind of the clinical trial and minimize the bias.

4) Drop-the-losers design: A drop-the-losers design allows dropping the inferior treatment groups or adding additional arms. A drop-the-losers design is useful in phase II clinical development especially when there are uncertainties regarding the dose levels [4,30-32].

5) Adaptive dose finding design: An adaptive dose finding design is often used to identify the minimum effective dose or the maximum tolerable dose for future clinical trials in early phase clinical development [33,34]. A Bayesian approach is usually considered in this kind of study [35,36].

6) Biomarker adaptive enrichment design: A biomarker adaptive enrichment design allows for adaptations based on the response of biomarkers. It involves biomarker qualification and standard, optimal screening design, and model selection and validation. It usually consists of two or three stages, where the first stage serves as a screening process for selecting a

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certain subpopulation, and the succeeding stages serve to distinguish the treatment effect from the control effect, within the selected (enriched) subpopulation.

7) Adaptive treatment-switching design: An adaptive treatment-switching design allows the investigator to switch a patient's treatment from an initial assignment to an alternative treatment if there is evidence of lack of efficacy or safety of the initial treatment. However, a high percentage of subjects switching treatment due to disease progression could lead to change in hypotheses, especially in oncology clinical trials, where the estimation of survival could be a challenge and sample size adjustment for achieving a desired power may be necessary.

8) Adaptive hypotheses design: An adaptive hypotheses design allows modifications in hypotheses based on interim analysis results [37]. For example, the hypothesis may switch from superiority to non-inferiority, or switch between the primary endpoint and the secondary endpoints.

9) Adaptive seamless phase II/III design: An adaptive seamless phase II/III trial design addresses the objectives that are normally achieved through separate trials in phase IIb and phase III of clinical development within one single trial. It is usually a two-stage design consisting of a learning stage (phase IIb) and a confirmatory stage (phase III). A typical approach is to power the study for the phase III confirmatory phase and obtain valuable information with certain assurance using confidence interval approach at the phase II learning stage. An adaptive seamless phase II/III design uses data from patients enrolled before and after the adaptation in the final analysis [38,39]. However, its validity and efficiency has been challenged [40]. Further, it is unclear how to perform a combined analysis if the study objectives are different at different phases [41].

10) Multiple adaptive design: A multiple adaptive design combines any of the above adaptive designs. However, the statistical inference for a multiple adaptation design is often difficult in practice.

Statistical Principles

The primary statistical concern in the FDA draft guidance (2018) is to control the overall familywise Type I error rate. Numerous statistical methods have been developed that theoretically handle adaptive design , e.g. p-value combination principle [e.g., 26,31,33,42], the conditional error approach [43], bias-adjusted Proschan and Hunsberger method [44], the weighted statistic approach [25,27], the "self-designing" and "variance spending" method [17,45], multistage adaptive design [31,46], the likelihood ratio test approach [47], the more recent work by Bartroff & Lai [48], etc. Liu & Chi [49] also gave a family of conditional error function in a different context.

It has been addressed that these approaches are interrelated [18-19,26,50-51]. These statistical methods can be categorized into two classes: combination test and conditional error function. In fact, the conditional error function approach can be looked at in terms of combination tests and vice versa [19].

1) Combination test principle. The combination test principle uses stage-wise test statistics which are combined according to a pre-defined combination function [e.g., 12,42].

2) Conditional error principle. The conditional error principle specifies that the conditional probability for a false rejection of the null hypothesis given that the previous stage is known. It states that any type of design modifications can be performed at any time of the trial as long as the conditional error of the new design does not exceed the conditional error of the pre-planned design [43,46].

Discussion

Adaptive design is all about flexibility. This flexibility comes from careful statistical planning. Given the complexity and uncertainty of adaptive design, thorough design evaluation may be required, e.g. conducting statistical simulations to evaluate the trial operating characteristics and Type I error probability, prespecifying statistical method for hypothesis testing and adaptation rules, etc. Although the statistical foundation of adaptive design is well established in past decades, adaptive design could create additional challenges in daily trial management or lead to trial operational complications, including but not limited to data collection, file documentation, access and communication of comparative interim results or adaptation decisions, maintenance of the trial blind, etc. Careful planning of dissemination of adaptation decisions to the sponsor, investigator, or trial participants may become critical to maintain the integrity of clinical trial. Additionally, the increased complexity of adaptive clinical trials may also lead to extensive interactions with the regulatory agencies, especially for late phase confirmatory trials.

In summary, adaptive design comes at a price of efficiency, careful statistical planning, and scientific interpretation. Good understanding in principles of adaptive design will facilitate the implementation of adaptive design, shorten the development timeline, and increase the probability of success in clinical development.

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