

# Adaptive Designs in Clinical Trials

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## Abstract

The traditional clinical trial is a rigid channel of drug development process. After successful Phase 1 trials and Phase 2 trial with sufficient efficacy and safety, the drugs goes into Phase 3 trials, where it is compared with a placebo or standard treatment (control). Performing this for each new drug separately need more manpower (patients/participant), money (financial resources), and time. On November 2019, the Food and Drug Administration issued a final guidance for the industries entitled, “Adaptive Designs for Clinical Trials of Drugs and Biologics.” They defined adaptive design as “a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.” In simple words, adaptive design means a design that permits modifications of “the trial procedures and/or statistical procedures of the trial” after its beginning without compromising the validity and the integrity of a trial. There are nine types of adaptive designs that includes adaptive randomization design, group sequential design, sample size re-estimation design, drop-the-losers design, adaptive dose finding design, adaptive treatment-switching design, biomarker-adaptive design, adaptive-hypotheses design, and adaptive seamless Phase II/III designs which has been explained in detail, in this review article. Although the concept of adaptive design has been there from long before but one of the major disadvantages it faces is the lack of uniformity.

**Keywords:** Adaptive designs, biomarker-adaptive design, sample size re-estimation design, seamless phase II/III design, sequential designs

## INTRODUCTION

The traditional clinical trial is a rigid channel of drug development process. After successful Phase 1 trials and Phase 2 trial with sufficient efficacy and safety, the drugs goes into Phase 3 trials, where it is compared with a placebo or standard treatment (control). Performing this for each new drug separately need more workforce (patients/participant), money (financial resources), and time.<sup>[1]</sup> Moreover, in the traditional approach, modifications of trial are not permitted, as it begins. Traditional clinical trials have three steps:

- Designing the trial
- To conduct the trial as per design
- Collecting and analyzing data according to a prespecified plan.

Hence, this design is simple but inflexible and doesn't permit any changes that may become necessary during trial. In contrast adaptive designs add an extra adapt loop to traditional design [Figure 1]. Multiple interim analysis in an ongoing trial, and based on these results pre-specified changes in the trial designs are allowed in adaptive design without losing the validity and integrity of the trial.

On November 2019, the Food and Drug Administration provided a final and complete guidance for the industries entitled, “Adaptive Designs for Clinical Trials of Drugs and Biologics.” They defined adaptive design as “a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.”

In simple words, adaptive design means a design that permits modifications of “the trial procedures and/or statistical procedures of the trial” after its beginning without compromising the validity and the integrity of a trial. The adaptation of “trial procedures” includes the inclusion/exclusion criteria, dose and duration of treatment, endpoints (definite or surrogate), diagnostic tools, laboratory testing procedures, and clinical responses evaluation procedure.<sup>[2]</sup> Moreover, “statistical

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procedures” includes study hypotheses, study design, sample size, randomization, data monitoring, interim analysis, and methods for statistical or data analysis.

This design makes a trial more flexible, productive and fast. For these flexibilities involved, such designs also known as “flexible designs.” However, this flexibility does not give all the freedom to modify it at any time for any purpose. In other words, the modification or adaptations should be preplanned and specified before initiating a study and should be based on interim data/analysis of the study itself.

## ADAPTIVE RANDOMIZATION DESIGN

In this design, probabilities of treatment assignment changes depending on already assigned participant in the trial, thereby helps in modification of randomization techniques. In simple words, it is a randomization procedure that analyses the patient’s previous treatment allocation and its responses, to determine the probability of future treatment allocation (of new patients).<sup>[3]</sup> The concept is allocating higher proportion of patient to the treatment arm that seems to be better in interim analysis [Figure 2]. Moreover, it is ethically ponder, sound, and attractive. The primary objective of this design is to reduce the number of treatment failures, increase the chance of trial

success and maximize power of the study. Different types of adaptive randomization are treatment adaptive randomization, covariate adaptive randomization, and response adaptive randomization. This type of design is not suitable for large trials or trials need longer duration of treatment, as it will increase the duration of trial more.

## GROUP SEQUENTIAL DESIGN

In this design, the sample size of the trial is not set in advance and trial may be stopped before completion, depending on the safety, efficacy or both, according to results of interim analysis. In other word, interim analysis is done at multiple pre specified points of time and data are evaluated. If the interim analysis shows significant results (beneficial or ineffective) or safety concerns (adverse effects) the trial can be stopped. However, the “stopping rule” (criteria for stopping) should be documented and explained before the initiation of trial.<sup>[4]</sup>

Group sequential design may offer an early conclusion than a conventional design does, thereby save time and cost. It is also ethically superior as it reduces the number of patients as well as duration of exposure to less effective/ineffective/harmful treatments.<sup>[5]</sup>

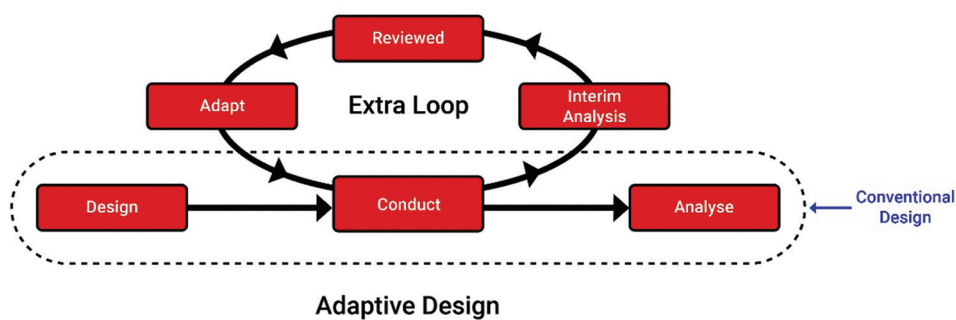


Figure 1: Conventional vis-a-vis adaptive design in clinical trials

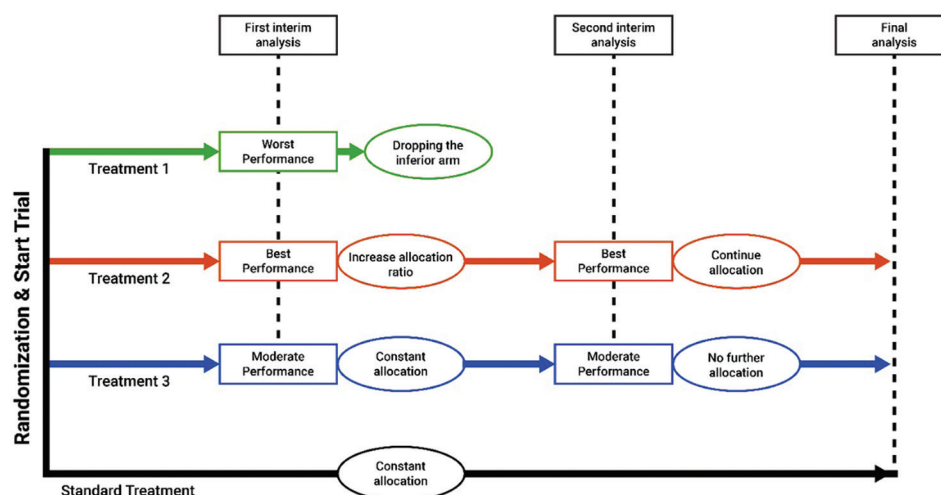


Figure 2: Adaptive randomization trial design

## SAMPLE SIZE RE-ESTIMATION DESIGN

In this design, sample size can be reassessed and adjusted during the study based on interim analysis, to ensure adequate power of the study. Apart from the effect size, other parameters such as standard deviation, coefficient of variation, drop-out rate are also taken as criteria for sample size adjustment during interim analysis. Appropriate sample size estimation for a clinical trial is often challenging. A smaller sample size may fail to detect difference between two treatments that actually exists.<sup>[4]</sup> Starting a study with small number of participant and then doing a sample size re-estimation at interim analysis is often misleading, as the observed difference at interim analysis based on a small number of participant may not be of statistical significance.

## DROP-THE-LOSERS DESIGN

In this design, inferior treatment arm(s) (groups) are dropped and new treatment arms are added. This design is usually used in Phase II clinical trial especially during dose finding. It is a two-stage design in which “selection criteria and decision rules” has important roles. On completion of the first stage, the inferior treatment arm(s) will be dropped on the basis of some pre-determined criteria (“selection criteria and decision rules”). The winners (better treatment arm/group) will then continue to the next stage.<sup>[3]</sup> This design is some time also referred as pick-the-winner designs.

## ADAPTIVE DOSE FINDING DESIGN

This design is often used in early phase clinical development (Phase 1/Phase 2) to identify the minimum effective dose and/or the maximum tolerable dose or to determine the appropriate dose level (by dose escalating) for the next phase clinical trials. Based on data at various interim analysis, randomization is focused toward better performing dose using continual re-assessment method and Bayesian decision criteria.

## BIOMARKER-ADAPTIVE DESIGN

Chen *et al.* define the biomarker adaptive trial design as “design which identify most suitable target subpopulation with respect to particular treatment, based on either clinical observation or known biomarker, and evaluate the effectiveness of the treatment on that subpopulation in a statistical valid manner.” In short, during interim analysis adaptations in this design is based on the “predictive biomarkers” status (positive or negative), which may include “adding or dropping” of treatment arms, identification of appropriate patients (as good or poor candidates) for selecting treatment, changes in sample size and proportion of allocation to different treatment arms, or refinement of the already included study population.<sup>[5]</sup>

This design involves identification, validation, and standardization of biomarkers that are related with clinical outcomes/response; development of appropriate screening methods for biomarker quantification, classifier development and its validation; and developing a “predictive model” between the particular

biomarkers and clinical outcome/response. This processes are often challenging (a “prognostic biomarker” indicates about the patient’s overall clinical outcome, regardless of treatments received, i.e., about the natural course of the disease, whereas “predictive biomarker”<sup>[6]</sup> gives information about the effect of a certain treatment or response to the treatment).

## ADAPTIVE TREATMENT-SWITCHING DESIGN

In this design, the investigator may switch a patient’s initial allocated treatment to a different treatment, depending on the efficacy or safety issues. Survival analysis is often challenging in this design especially in oncology trial.<sup>[3]</sup> If proportion of treatment switching is high it could affect the study hypotheses and may lead to change in hypotheses. Adjustment of sample size is necessary to maintain the desired power of the study here.

## ADAPTIVE-HYPOTHESES DESIGN

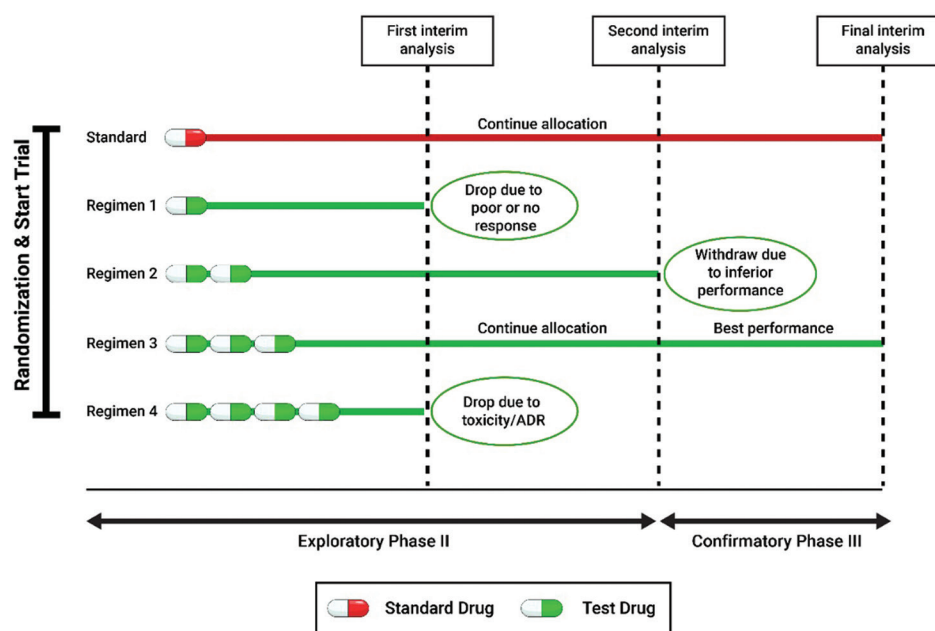
In this design, modifications of hypotheses are done based on results from interim analysis.<sup>[7]</sup> For examples switching from superiority to a noninferiority hypothesis or the switching between primary and secondary study endpoints. These modifications of hypotheses are mostly considered prior to “database lock” and/or “data unblinding.” Here, also the adjustment of sample size is necessary to maintain the desired power of the study.<sup>[8]</sup>

## ADAPTIVE SEAMLESS PHASE II/III DESIGN

A seamless design joins two different trials (such as Phase 2 and Phase 3) into single trial, also known as “operationally seamless.” An adaptation in seamless design permits to use data before and after adaptation and data of both Phase 2 and Phase 3, during final analysis, this is also known as “inferentially seamless.” Primary objective of this design is to combine dose selection and confirmation phase into one trial. This design minimized time and cost and often use in rare disease. For example, in the first stage of design (Phase 2b) patients are randomized between treatments (multiple dose level) arms and a control arm (standard care/placebo). At the end of the first stage (Phase 2b), optimal dose is selected based on interim data (definitive or surrogate marker, primary endpoint, or early achieving of endpoint or progression-free survival). The selected best effective arm is continued to the second phase (Phase 3). New participants enrollment continues only for the selected dose and control arm.<sup>[9]</sup> At the end of the Phase 3, comparative efficacy analysis is performed between the treatment and control arm. All data from the selected arm and control arm is used for final analysis [Figure 3]. Using all data from Phase 2b and Phase 3 reduce the error and increase the trial integrity and power of the study.

## MULTIPLE ADAPTIVE DESIGN

It is the combinations of, any of the above adaptive designs. Commonly used multiple-adaptation designs are a combination



**Figure 3:** Adaptive seamless Phase II/III design

**Table 1: Examples of trials using various adaptive designs**

| Trial design                          | Full name of the trial                                                                                                                                                                                                                                        | Drug evaluated                                                                                                                                     |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Adaptive randomisation                | Low-dose dexamethasone as a treatment for women with heavy menstrual bleeding (DexFEM): Protocol for response-adaptive randomized placebo-controlled dose-finding parallel group trial                                                                        | Dexamethasone                                                                                                                                      |
| Group sequential design               | Carotid Artery Implant for Trapping Upstream Emboli for Preventing Stroke in Atrial Fibrillation Patients (CAPTURE)                                                                                                                                           | Abciximab                                                                                                                                          |
| Sample size re-estimation             | Phase III Randomized Study of Immediate Versus Luteal Phase Adjuvant Oophorectomy and Tamoxifen in Premenopausal Women With Hormone Receptor-positive Breast Cancer                                                                                           | Tamoxifen                                                                                                                                          |
| Drop-the-losers design                | Telmisartan and insulin resistance in HIV (TAILoR): protocol for a dose-ranging phase II randomized open-labeled trial of telmisartan as a strategy for the reduction of insulin resistance in HIV-positive individuals on combination antiretroviral therapy | Telmisartan                                                                                                                                        |
| Adaptive dose finding design          | Rationale and study design of the adaptive study of IL-2 dose on regulatory T cells in type 1 diabetes (DILT1D) : a non-randomized, open label, adaptive dose finding trial                                                                                   | Interleukins-2                                                                                                                                     |
| Biomarker-adaptive design             | Molecular selection of therapy in colorectal cancer: A molecularly stratified randomized controlled trial program (FOCUS4)                                                                                                                                    | 1. Panitumumab with or without MEK inhibitor<br>2. Aspirin<br>3. AKT inhibitor and MEK inhibitor<br>4. HER 1, 2 and 3 inhibitor<br>5. Capecitabine |
| Adaptive seamless phase II/III design | Implementing the EffTox (Efficacy and toxicity-Bayesian adaptive design) dose-finding design in the Matchpoint trial                                                                                                                                          | Optimal dose of Ponatinib in CML patients (with conventional chemotherapy)                                                                         |
| Adaptive seamless phase I/II design   | A novel phase I/IIa design for early phase oncology studies and its application in the evaluation of MK-0752 in pancreatic cancer                                                                                                                             | MK-0752 (Investigational medicinal product)                                                                                                        |
| MAMS trial                            | STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy                                                                                                                                                            | Celecoxib<br>Docetaxel<br>Prednisolone<br>Zoledronic acid<br>Abiraterone<br>Radiotherapy Enzalutamide<br>Metformin<br>Transdermal Oestradiol       |

of (i) adaptive group sequential design, drop-the-losers design, and adaptive seamless trial design and (ii) adaptive dose-escalation design with adaptive randomization. Statistical analysis and inference of a multiple-adaptation design is very difficult and often challenging.<sup>[9]</sup> Hence, it is better to perform a clinical trial simulation to evaluate the performance of the proposed multiple adaptive design before taking a decision for the same. Examples of trials using various adaptive designs has been shown in Table 1.

## ADVANTAGES

Flexibility to change in different study/statistical parameters during trial course according to pre-specified criteria and time point. For example, adjustment of sample size as follows:

- This designs reduce overall development time (freedom to premature stop) and increase chance of success than conventional designs
- Ethically superior as this designs increase the chance of exposure to an effective treatment/dose and reduce exposure to ineffective/hazardous dose<sup>[10]</sup>
- May be stopped pre maturely as per concern of safety, efficacy, or both. This may reduce overall development cost of pharma industries.

## DISADVANTAGES

- Need to convince the regulatory authority and permission for adaptive design
- Before starting an adaptive trial, evaluation of its success is to be assessed by modeling and simulation design
- Initial (before starting an adaptive trial) requirement of plans, cost, time, and intelligence is more than a conventional design. And also more difficult to implement properly<sup>[10]</sup>
- Adaptation may introduce biases
- Controlling type 1 error and confidence interval coverage is challenging in statistical analysis, treatment effect estimation is also difficult.

## CONCLUSION

Adaptive design has advantages over conventional design, as it offers some flexibility (preplanned) in modifications to different elements of a study, and makes it more efficient and fast. Adaptive design is also be useful in early-phase exploratory trials (Phase 2), i.e., in dose finding as well as late confirmatory phase (Phase 3) and Phase 4. This design is ethically superior as fewer patients are exposed to suboptimal treatments or drug related adverse effect. However, adaptive design is not without risk of adding bias. Hence, it is advisable that study should be carefully designed with pre specified adaption plans.

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## Conflicts of interest

There are no conflicts of interest.

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