Paper ST09

Handling Multiple Adaptations in One Clinical Trial

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ABSTRACT

USFDA has defined Adaptive Designs 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. These types of designs are becoming more common to take advantage of their flexibility and benefits. However, these planned modifications will have a direct impact on statistical principles used for designing, execution and analysis of the clinical trial and it is vital to prevent the inflation of type I error, estimation of sample size and combining data from multiple phases.

This paper will discuss the benefits/risks of adaptive design and statistical challenges when group sequential design, adaptation to sample size and adaptation to treatment arm selection with multiple primary endpoints are considered for a clinical trial. Discussion on different types of adaptive designs used in the past few years by sponsors will also be covered.

INTRODUCTION

It is not uncommon to modify the clinical trials or statistical procedures during the conduct of the trial based on the review of the interim data. The purpose is not only to efficiently identify clinical benefits of the test treatment under investigation, but also to increase the probability of success of clinical development. Trial procedures are referred to as the eligibility criteria, study dose, treatment duration, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluability, and assessment of clinical responses. Statistical procedures include randomization, study design, study objectives/ hypotheses, sample size, data monitoring and interim analysis, statistical analysis plan, and/or methods for data analysis. The adaptations made to the trial and/or statistical procedures lead to adaptive design methods that are designed and regulated in such a way that the validity and integrity of the trial is maintained.

TYPES OF ADAPTIVE DESIGN

There can be many types of adaptive designs and following are some of the common adaptations to design:

- Group Sequential Design
- Sample Size re-estimation
- Adaptive Seamless Design
- Adaptive Dose Finding
- Biomarker Adaptive
- Master Protocol

Adaptations to study design has potential advantages and challenges attached to it as mentioned below and listed in FDA guidance document as well:

Advantages	Challenges
Statistical Efficiency	Need of specific analytical methods
Ethical considerations	Increased maximum sample size
Improved understanding of Drug Effects	Logistical challenges to ensuring appropriate trial conduct and trial integrity
Acceptability to stake holders	Difference in results before and after adaptation

MULTIPLE ADAPTATIONS IN ONE TRIAL

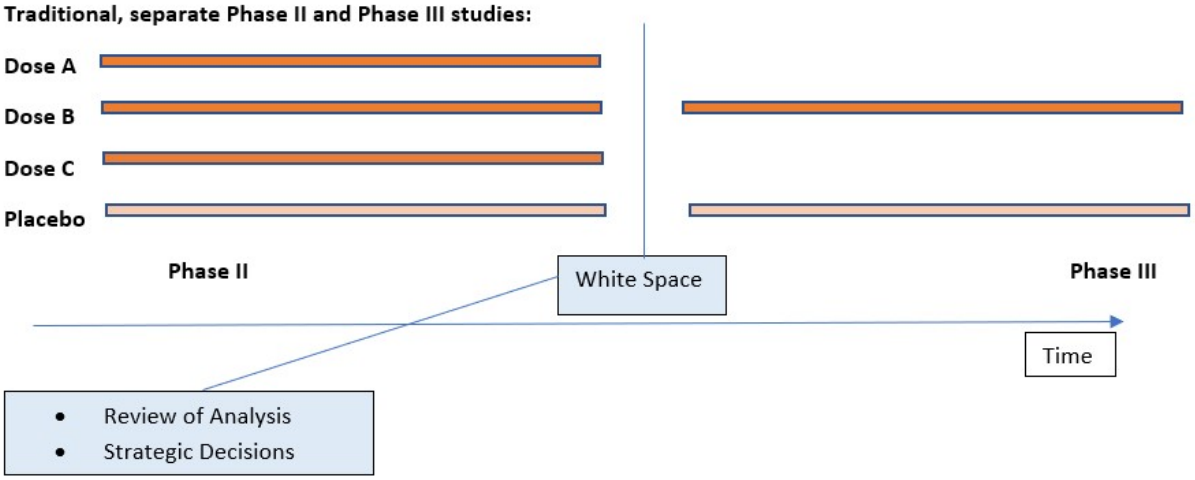
We will consider a trial with following adaptations to discuss statistical principles and challenges:

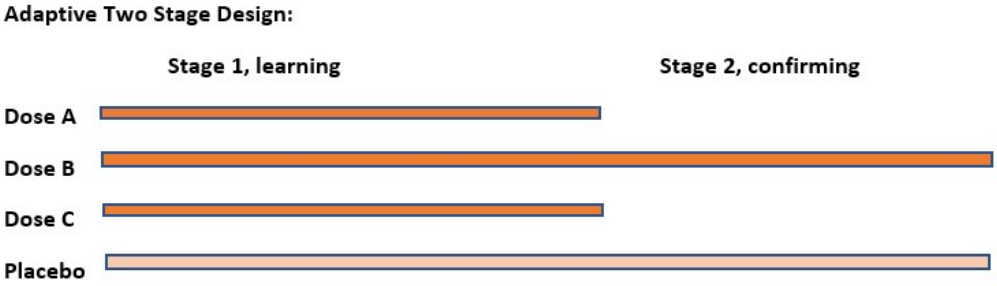
- Interim analysis (not to prove efficacy)
- Sample Size re-estimation
- Dose Finding

This type of design adaptations will be fit for Adaptive Seamless Design

In clinical trials we have different phases of experiments. Phase IIb is where generally we are to finalize the dose and move ahead to test efficacy (Phase III) of the finalized dose. An adaptive seamless phase II/III trial design is referred to as a program that addresses within single trial objectives that are normally achieved through separate trials in phase IIb and phase III of clinical development.

SEAMLESS DESIGN AND ADAPTIVE SEAMLESS DESIGN





SEAMLESS DESIGN

A clinical trial design which combines into a single trial objective which are traditionally addressed in separate trials (operationally seamless). There are two stages of this design wherein in the first stage different doses in Phase II are tested and in the *white space* (see Figure 1) after review of analysis it is determined which dose is the best and then the stage 2 is carried out which is Phase III. Participants in seamless design are enrolled separately for each stage i.e., Phase II and Phase III and review of analysis is totally exclusive of each other. Let's say for each treatment arm in Phase II, 50 participants are enrolled which makes the sample size of Phase II, 200 participants i.e., n_1= 200. After dose selection procedure during the *white phase*, new participants are enrolled for Phase III trial say 100 participants each for Dose B (selected dose) and Placebo i.e., n_2= 200 (See Figure 1). Thus, the overall sample size of the trial will be n_1+n_2= 400 participants.

ADAPTIVE SEAMLESS DESIGN

An adaptive seamless trial is in which the final analysis will use data from participants enrolled before and after the adaptation (inferentially seamless). So, in Stage 1/ Phase II, 50 participants will be taken for each treatment arm thus sample size for Stage 1 is 200 i.e., n_1= 200. An interim analysis will be performed for dose selection for Stage 2/ Phase III of the experiment. Suppose Dose B (See Figure 1) is selected as the dose to be tested against Placebo in Stage 2/ Phase III, instead of say adding 100 participants to each treatment arm we add 50 participants each to the two treatment arms which are Dose 2 and Placebo. So, for Stage 2/ Phase III sample size will be 100 participants i.e., n_2= 100. So, for Stage 2/ Phase III, there will be 100 participants each in the two treatment arms (data available for 50 participants each from Stage 1/ Phase II for Dose 2 and Placebo and new enrolled 50 participants each for Stage 2/ Phase III). The total sample size for the trial will be n_1+n_2=300 participants.

<u>Primary objective of adaptive seamless design:</u>

- to combine "treatment selection" and "confirmation" in one trial
- enrol patients into the trial
- during the trial, select the optimal dose based on interim data, early read-out of primary endpoint
- enrolment continues only on the selected dose and the comparator arm
- all data from chosen arm and comparator is used in final analysis, using novel statistical methods for combining evidence from first and second stage to control of false positive error rate and maintaining trial integrity

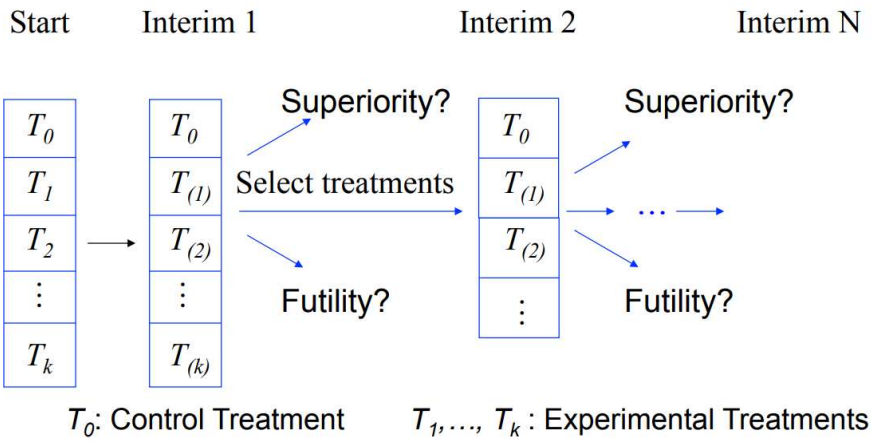
<u>Benefits of using adaptive seamless design:</u>

- clinical trials using adaptive seamless Phase II/III design are quicker to complete i.e., effective drug is available earlier for patients
- smaller number of participants required overall as compared to seamless trials

GENERAL ASSUMPTIONS

We consider seamless phase II/III clinical trials that compare K treatments with a common control in phase II then test the most promising treatment against control in phase III. The final hypothesis test for the selected treatment can use data from both phases, subject to controlling the familywise type I error rate.

We suppose patient responses are normally distributed with known variance σ^2 and means μ_0 on the control arm and μ_i, $i = 1,\ldots,K$, on treatment arms, with a high mean indicating a successful treatment. In this paper in all the examples we discuss, we will assume μ_i, $i = 1, 2$ (comparison of two treatment arms against placebo).



As we understand from the study design there will be two stages and at each stage, we will have different set of hypotheses.

Moving forward, we will refer Phase II as Stage 1 and Phase III as Stage 2 in this paper.

Stage 1 hypothesis- comparing two doses with placebo
Null hypothesis $H0^1$: Dose 1 <= Placebo $H0^2$: Dose 2 <= Placebo
Alternate hypothesis HA_1 : Dose 1 > Placebo HA_2 : Dose 2 > Placebo

Stage 2 hypothesis- comparing the promising dose with placebo, suppose Dose 1 is selected to move to stage 2.
Null hypothesis H0: Dose 1 <= Placebo
Alternate hypothesis H1: Dose 1 > Placebo

STATISTICAL CONSIDERATIONS

TYPE I ERROR INFLATION

In the design described above, we will discuss two potential reasons for type 1 error inflation 1) due to multiple hypothesis testing 2) due to the type of design which is adaptive seamless design

Sources of potential inflation of Type I error	Error controls
Multiple hypothesis testing	Multiple testing methodology, e.g., closed test procedures, graphical approach
Adaption of design features and combination of information across trial stages	Combination of p-values, e.g., inverse normal method, Fisher's combination test

INFLATION DUE TO HYPOTHESIS

As per our assumption, in this paper we have two treatment arms versus placebo which leads to multiple hypothesis testing.
So here we have two hypotheses to test in stage 1 and let's say we set α at 5%.
Test 1: $H_{1:}$ Dose 1 vs Placebo
Test 2: $H_{2:}$ Dose 2 vs Placebo
If both the doses are completely independent, then we can say that the overall chance of making Type I error is:
Test 1: Chance of making Type I error in Test 1: 1 - 0.05= 0.95
Test 2: Chance of making Type I error in Test 2: 1 - 0.05= 0.95
Overall chance of not making Type I error= 0.95 X 0.95= 0.9025
So, the overall experiment wise error rate α is 1 - 0.9025= 0.0975 ≈ 0.01

This means that there is an α inflation caused by such testing. There are methods to handle this inflation in Type I error.

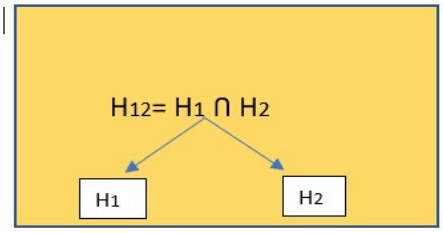
Bonferroni method for type I error adjustment for multiple hypothesis

To control Type I error rate in the overall experiment which has two testing points or hypothesis, we need to divide the alpha (α) into two parts. So, if we have two hypothesis tests in an experiment, we divide α by 2 (α/2), similarly if there are 3 hypothesis tests in an experiment, we divide α by 3 (α/3) and so on. So, this approach of α adjustment depending upon number of hypothesis (m) tests within an experiment (α/m) is called the Bonferroni method of type I error adjustment.

Bonferroni with Closure Principle

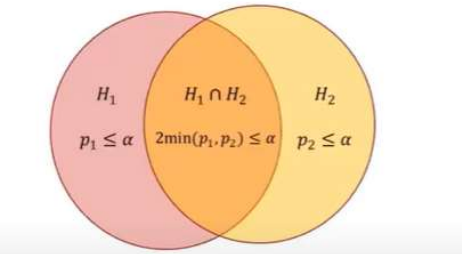
To be able to test multiple hypothesis and control α inflation another method is to apply closure principle to Bonferroni method. Suppose there are k hypotheses H1,…., Hk to be tested and the overall type I error rate is α. The closed testing principle allows the rejection of any one of these elementary hypotheses, say Hi, if all possible intersection hypotheses involving Hi can be rejected by using valid local level α tests; the adjusted p-value is the largest among those hypotheses. It controls the error rate for all the k hypotheses at level α in the strong sense.

Suppose there are three hypotheses H1, H2, and H3 to be tested and the overall type I error rate is 0.05. Then H1 can be rejected at level α if H1 ∩ H2 ∩ H3, H1 ∩ H2, H1 ∩ H3 and H1 can all be rejected using valid tests with level α.
Simply saying, to reject any one of the hypotheses we need to reject all the intersection hypothesis, as well using a suitable combination function. This property is called the closure principle. If we use a method that satisfies this closure principle, then we will have a test procedure that will control type 1 error strongly.
Taking the example of three treatment arms, Dose 1, Dose 2 and Placebo:
H_1= Dose 1 <= Placebo
H_2= Dose 2 <= Placebo
H_{12}=H_1 ∩ H_2= Dose 1 > Placebo < Dose 2



H1 can only be rejected at level α if H12 is also rejected at α

Multiplicity for intersection hypothesis testing can be handled by using adjusted p-values example for Bonferroni use p_{12}= 2 X min (p_1, p_2)



Suppose p-value of Dose 1= p_1= 0.02
Suppose p-value of Dose 2= p_2= 0.067

- p_{12}= 2 X min (0.02, 0.067)
- p_{12}= 2 X min (0.02) = 0.04

So, from this example H_1 can only be rejected if and only if p_1 and p_{12} both are less than α

INFLATION DUE TO TYPE OF DESIGN

In adaptive seamless design, the same hypothesis is re-tested multiple times (e.g. interim and final analyses) which may lead to α inflation.

In such design of trial, we are combining data from two stages of a single trial, which means data that is collected at stage 1 and stage 2, and both used for final analyses. Thus, any hypothesis testing done during stage 1 of the trial has to be accounted while doing analyses of stage 2 of the trial.
Example Dose 1, Dose 2, and Placebo.

Dose 1 is more promising dose and hence is taken ahead for stage 2 of the trial. Part of the data to be analyzed for Dose 1 against Placebo, comes from stage 1 of the trial (reminder: more participants are added in the promising dose and tested for efficacy).
This means that there will be an α inflation caused by such study design.

p-value combination method

There are several ways by which p value from two stages can be combined but in practice there are two methods that

are widely used.
Fisher's product: C (p_1, p_2) = p_1p_2 (as shown by Bauer and Kohne 1994)
Inverse normal method:
(φ^{-1}) where φ is probability mass function for the normal distribution

- n1= Sample size from Stage 1
- n2= Sample size from Stage 2
- w = n1/ (n1+n2) will be weight

C (p_1, p_2) = $\sqrt{w}\varphi^{-1}$ (1-p_1) + $\sqrt{1-w}$ φ^{-1} (1-p_2) ~ N (0,1)

This inverse normal method for defining the combination function is often used in practice and is a common choice since it is flexible and allows for adaptation, including unblinded sample size re-estimation.
Closure principle would need to be used at stage 2 if there are more than one hypothesis that need to be tested.

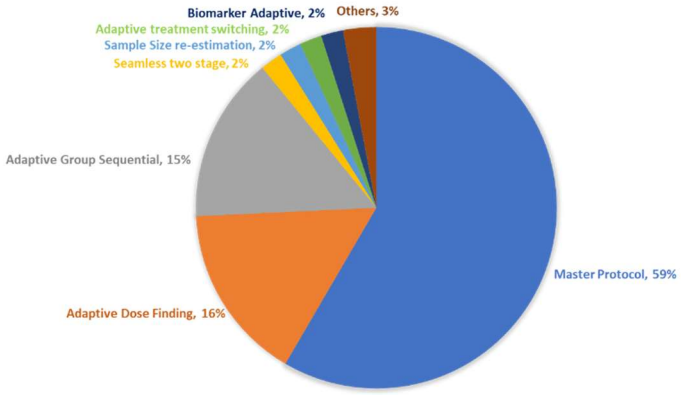
SAMPLE SIZE RE-ESTIMATION

Sample size estimation at start of study and at the end of stage 1 needs to be performed with simulations and considering following points:

- Assume treatment effects in a range based on literature or previous studies.
- Simulate the data for stage 1 and stage 2 based on range of treatment effects and possible sample size range.
- Minimum Sample size needed to detect clinically meaningful trend and dose selection shall be considered for stage 1.
- Stage 2 sample size shall be provided in a range with dependency on results/conditional power at the end of stage 1(interim analysis).
- Sample size shall be re-estimated at the end of stage 1 using observed conditional power.

ADAPTIVE DESIGN TRIALS IN PAST

Adaptive Designs in clinical trials have been used for a long time now. Following figure shows that type of adaptive designs used since 1998. Master Protocol Design is the most common one where one therapy is used for multiple indications or vice a versa. There can be a separate discussion of different types of Master Protocol Design.



Shuhang Wang et.al. (2021) have shown the increase in number of trials starting every year with some type of adaptive design. Increasing numbers of adaptive clinical designs have brought an urgent need for guidance, consensus, and regulations due to the notable differences between adaptive trials and traditional trials. Countries or regions like European (medicine agency,2007) and U.S(Food and Drug Administration department,2010) has published guidelines and experience consecutively. In May 2020, China Center for drug evaluation (CDE) initiated guideline on Adaptive Designs for Clinical Trials, recognizing the validity of adaptive trial, and providing references to facilitate the complicated design.

CONCLUSION

Adaptive designs have become more and more popular with advantages of statistical efficiency, ethical considerations, and cost effectiveness. However, it becomes equally important to handle following aspects carefully to get reliable results:

- Controlling the chance of erroneous conclusion
- Analytical methods to estimate treatment effects
- Proper trial planning before starting the trial
- Maintaining trial conduct and integrity

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