

Abstract and Definitions

Introduction

Adaptive designs (ADs) can improve the efficiency of clinical trials, allowing for an adjustment to the duration of the trial, the endpoint, sample sizes, or elimination/addition of treatment arms. These types of designs are becoming more common in order to take advantage of their flexibility and benefits. However, planning and executing adaptive designs can be tricky for a variety of reasons and it is vital to prevent the inflation of type I error when examining the data at an interim analysis. This requires up-front planning and discussion between the statistical team and the client, in order to clearly define rules for adaptations to be made at the time of the interim analysis.

What are Adaptive Designs?

An AD allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. These designs allow for mid-trial dose selection (dropping futile doses, introducing new doses, etc.) and adjustment of sample sizes/allocation or hypotheses to achieve greater power. These modifications must be pre-planned, before unblinding of data occurs.

Benefits/Risks

Benefits: earlier detection of efficacious/futile drugs, pre-planned modifications cut down on time spent writing amendments, ability to respond to unexpected results or events, saves money and subjects less patients to futile drugs.

Risks: difficult to control Type 1 error rate, credibility of trial may be in question, designs can be ultra-complex and require Bayesian techniques, simulations

Planning the Adaptive Design – Prior Assumptions

First, decide if AD is appropriate for the trial – is it feasible, practical?

Assumptions and pre-determined factors:

- Type I error rate (α)
- True underlying distributions for mean/standard deviation
- Total sample size, sample size when IA will be performed
- Desired conditional power (CP) during the trial

Planning and Executing

Planning the Adaptive Design – Protecting Inflation of Type I Error

When looking at the data multiple times, keep in mind **multiplicity** must be considered. In this case, we are examining multiple doses versus placebo, and looking at the data at the IA and at the end of the trial.

The overall α level set at the beginning of the trial (example: 0.05) must be protected. At each stage, adjusted p-values will be calculated using a multiplicity adjustment such as Simes, Sidak, Bonferroni, etc. if more than one comparison is being examined within the stage.

Once these p-values are calculated, they can be combined via the Inverse Normal Method to get an overall p-value for the trial. This is calculated as follows: $p = 1 - \Phi(w_1 \Phi^{-1}(1 - p_1) + w_2 \Phi^{-1}(1 - p_2))$ where:

$$w^{(1)} = \sqrt{\frac{n^{(1)}}{n}} \quad w^{(2)} = \sqrt{\frac{n^{(2)}}{n}} \quad n^{(1)} = \text{sample size at the IA} \\ n^{(2)} = \text{sample size for post-IA data} \quad n = \text{total sample size for entire trial}$$

$\Phi(\cdot)$ = cumulative distribution function of the standard normal variable

p_1 = p-value from the IA

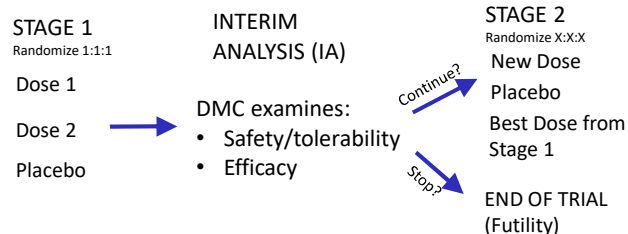
p_2 = p-value from end of trial

Planning the Adaptive Design – Understanding Conditional Power

Conditional power (CP) is the probability that the final study result will be statistically significant, given the data observed thus far. This will guide what decision you make at the IA – and whether to adjust the sample size.

CP	Zone	Decision
CP < 30%	Unfavorable	No SSR
30% ≤ CP < 80%	Promising	SSR
CP ≥ 80%	Favorable	No SSR

Executing the Adaptive Design – Example



Our example is used to examine multiple treatments versus control, integrated into one confirmatory trial, instead of multiple clinical trials.

First: Determine the purpose for designing an AD

The type of AD we will use in this example is a multi-arm (4 treatment) multi-stage (2-stage) dose-finding design. The purpose for utilizing an adaptive design here was in order to drop ineffective (or less effective) doses, introduce a new dose, stop for futility, and/or adjust the sample size allocation to each arm in order to boost the power.

Executing the Adaptive Design – Example

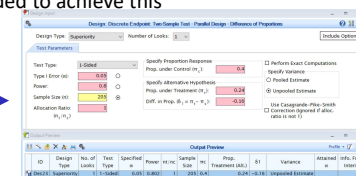
Second: Establish prior assumptions and decisions

- Type I error rate of $\alpha = 0.05$, one-sided test
- True incidence rate for Placebo = 0.40, Treatment = 0.24 (40% reduction)
- Desired power = 80% for final comparison between New Dose (Stage 2) versus Placebo, calculate sample size needed to achieve this

N=103/arm will achieve

~80% power for

New Dose vs Placebo



- Perform IA when 120 patients total (40/arm in Stage 1) have reached a particular milestone – decision made based on availability of drug

Third: Simulate design 10,000 times to determine operating characteristics

- Using EAST software, specify sample size/weights at time of IA, conditional power bounds (30% and 80%) for promising zone, multiplicity adjustment (Sidak) to ensure preservation of Type I error and total sample size if re-estimation should occur
- Simulate to obtain operating characteristics:
 - For total simulations, how many times did the following occur: futility, efficacy, promising zone reached (sample size re-estimation)? What was average total sample size, max total sample size?

Fourth: Outline decisions to be made by DMC

- FUTILITY:** If both Dose 1 and 2 show incidence rates equal to or greater than placebo, only Stage 2 New Dose & Placebo will move forward into Stage 2
- UNFAVORABLE:** If CP < 30%, N=50 randomized to Stage 1 most efficacious/safe Dose, N=103/arm will be randomized to Stage 2 New Dose and Placebo
- PROMISING:** If 30% ≤ CP < 80%, sample size will be boosted to N=150/arm for Stage 1 most efficacious/safe Dose and Placebo, N=103 will be randomized to Stage 2 New Dose
- FAVORABLE:** If CP ≥ 80%, N=50 randomized to Stage 1 Best Dose, N=103/arm will be randomized to Stage 2 New Dose and Placebo

Conclusions

When presenting the option of an AD, first outline the benefits versus risks and discuss prior assumptions. Once overall sample size is determined for a desired power, and IA time is determined (based on availability of drug or sample size that will help obtain a higher probability of stopping for efficacy, for example), it is helpful to illustrate the performance characteristics using EAST to determine probability of each decision occurring given the prior assumptions and up-front decisions.

References

Mahajan, R and Gupta, K. Adaptive Design Clinical Trials: Methodology, Challenges and Prospect: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2941608/#CIT43>