

ADAPTIVE DESIGN – BETTER BEND THAN BREAK

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INTRODUCTION

- Adaptive design permits modifications to the trial and/or statistical procedures after the trial has begun without compromising its validity and integrity.

Advantages

- Permits the trial to adjust using the data accrued during the trial
- Cost-effective
- Reduce resource use
- Improve time efficiency

Disadvantages

- Gains in efficiency may result in loss in other aspects
- Chance of error conclusions
- Results may differ after adaptation

COMMONLY USED TECHNIQUES

Adaptive
Randomization
Design

Sample Size Re-
estimation
Design

Hypothesis-
Adaptive Design

Adaptive Dose
Finding Design

Suspending the
Efficacy
Evaluation

Drop-the-Loser
Design

Group Sequential
Design

Adaptive
Treatment-
Switching Design

ADAPTIVE RANDOMISATION DESIGN

Probability of treatment assignment changes according to assigned treatments of patients already in the trial.

The purpose is to increase the probability of success.

Commonly applied adaptive randomization procedures include

- Treatment-Adaptive Randomization.
- Covariate-Adaptive Randomization.
- Response-Adaptive Randomization.

Limitation - It is not possible to use this adaptation in a trial of long duration

ADAPTIVE RANDOMISATION DESIGN

Covariate adaptive randomization

- The covariate adaptive randomization (CAR) method is used to reduce the imbalance between the covariates in the treatment groups.
- Allocation probability for this method is changed over time during the trial.

Frane method

- The Method aims to balance the treatment groups by assigning the next patient to a treatment group so that the imbalance among the covariates is the least.

Pearson's chi-squared test

- A test of goodness of fit checks whether there is any difference between observed frequency distribution and theoretical frequency distribution.

$$\chi_c^2 = \sum_i \frac{(O_i - E_i)^2}{E_i}$$

ADAPTIVE RANDOMISATION DESIGN

Case Study

- Study Explanation - A phase II, prospective, multi-center, randomized, 4-week, double-blind, placebo-controlled, designed to determine the safety and tolerability of fixed oral dose of study treatment in patients with chronic schizophrenia along with their regular medication.
- Study objective - To implement Covariate Adaptive Randomization based on the interim analysis.

Data Description

The data available is the covariate information of 60 subjects.

Covariates :- Gender and Country

Covariate	Level	Treatment Group	Count
1 (Gender)	1 (Male)	Treatment A	18
1 (Gender)	2 (Female)	Treatment A	14
2 (Country)	1 (USA)	Treatment A	17
2 (Country)	2 (UK)	Treatment A	15
1 (Gender)	1 (Male)	Placebo	15
1 (Gender)	2 (Female)	Placebo	13
2 (Country)	1 (USA)	Placebo	12
2 (Country)	2 (UK)	Placebo	16

ADAPTIVE RANDOMISATION DESIGN

Method

Step 1

Temporarily assign the new patient to treatment group A first.

Step 2

Calculate the Pearson's χ^2 Goodness-of-Fit test statistic for the covariate groups to which the new patient would belong.

Step 3

Identify the maximum χ^2 test statistic among all the covariate groups.

Step 4

Now temporarily assign the new patient to Placebo group and repeat steps 1 – 3

Step 5

Identify the minimum χ^2 test statistic over all the identified test statistics and assign the new subject to that corresponding treatment.

ADAPTIVE RANDOMISATION DESIGN

		Treatment A N _A =32	Placebo N _B =28
Gender	Male	18	15
	Female	14	13
Country	USA	17	12
	UK	15	16

	Treatment A	Placebo	χ^2
Male	19	15	0.47
UK	16	16	0

	Treatment A	Placebo	χ^2
Male	18	16	0.11
UK	15	17	0.12

The new patient will be assigned to Placebo because the covariates have less imbalance when the patient is in Placebo.

Result

Using SAS code and the prior information available on covariates of the trial, we assigned the patient to 'Treatment A' or 'Placebo' based on the nature of covariate of new patient.

SAMPLE SIZE RE-ESTIMATION (SSRE)

- Sample size re-estimation is a design that allows us to increase the samples size based on the updated knowledge.

Blinded Sample Size Re-estimation

The sample adjustment is based on the (observed) pooled variance at the interim analysis to re-calculate the required sample-size.

Unblinded Sample Size Re-estimation

The effect size and its variability are re-assessed, and sample-size is adjusted based on the updated information.

SAMPLE SIZE RE-ESTIMATION (SSRE)

Case study

In this case study, it's intended to assess the results of blinded and unblinded SSR on the same data.

Data Description

Interim analysis data for Phase 2 Placebo controlled study to compare the change in total PANSS Score at week 4 was used.

From protocol, mean (SD) change from baseline at Day 28 for PANSS Total score was greater for Treatment A than Placebo. Numerically greater improvement with Treatment A vs Placebo.

When the interim analysis was performed, about 60 subjects completed week 4 assessment.

SAMPLE SIZE RE-ESTIMATION (SSRE)

Method

Initially, the sample size is calculated using the classical method, using the formula

$$n = \frac{2(z_{\alpha} + z_{\beta})^2 \sigma^2}{(\mu_1 - \mu_2)^2}$$

Unblinded Sample size re-estimation

Sample-size adjustment based on the effect-size ratio

$$N = \left| \frac{E_0}{E} \right|^a N_0$$

N is the newly estimated sample-size per group, N_0 is the initial sample-size per group.
E is the observed effect size, E_0 is the initial effect size used for sample size estimation.
 $a > 0$ is a constant.

Where, $E = \frac{\hat{\mu}_2 - \hat{\mu}_1}{\sigma}$

SAMPLE SIZE RE-ESTIMATION (SSRE)

Blinded sample size re-estimation

Pooled variance can be considered as an estimate of common variance when we assume that different populations have the same variances.

A common variance for sample size re estimation is calculated

$$S_{final}^2 = S_{pooled}^2 - \frac{n_1}{4(n_1 - 1)} \Delta^{*2}$$

Where Δ^* is the assumed mean difference.

Where the unbiased estimate of variance (Pooled sample variance) is calculated using:

$$S_{pooled}^2 = \frac{1}{n_1 - 1} \sum_{i,j} (X_{ij} - \bar{X})^2$$

The sample size was then recalculated with the updated pooled variance.

SAMPLE SIZE RE-ESTIMATION (SSRE)

Results

- There was a significant increase in the effect size along with the variance as compared to the initial assumption observed, which results in decrease of the sample size when unblinded SSR was used.
- The Blinded SSR results in an increase of sample size which is not practically possible since only the increase in variance was used for sample size estimation.
- Unblinded SSR resulted in improved power, while Blinded SSR resulted in overpowering as sample size increased significantly than required.

CONCLUSION

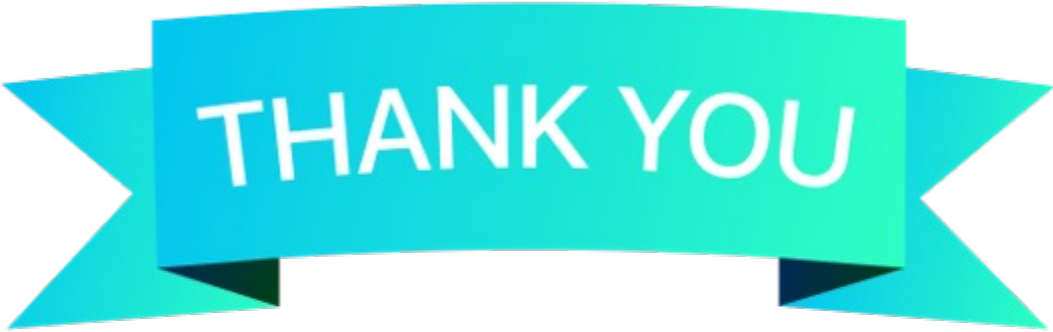


Discussed two approaches that we have used in the trial data adaptive design.

Adaptive design can provide a second life to a clinical study.

Hope this is a good starting point, but we will need far more insight on the topic to be executed.

We are working on the rest of the Adaptive Design techniques.



THANK YOU



Any Questions ?