



PHUSE 2023

Statistical Challenges with Multiple Adaptations in One Clinical Trial

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AGENDA

- Definition of Adaptive Design
- Adaptive Design
- Challenges
- Multiple Adaptations Example
- Statistical Considerations
 - Type I Error Inflation
 - Sample Size
- Adaptive Design Trials in past

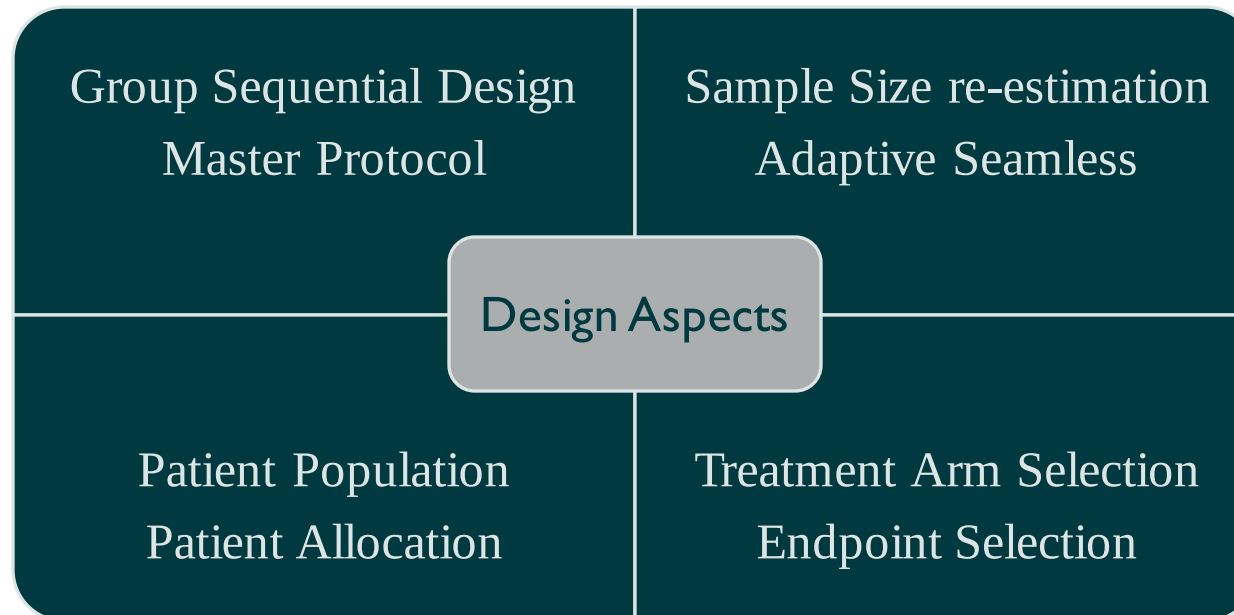


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Definition of Adaptive Design

- 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.



Advantages

- Statistical efficiency
- Ethical considerations
- Improved understanding of drug effects
- Acceptability to stake holders



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Challenges

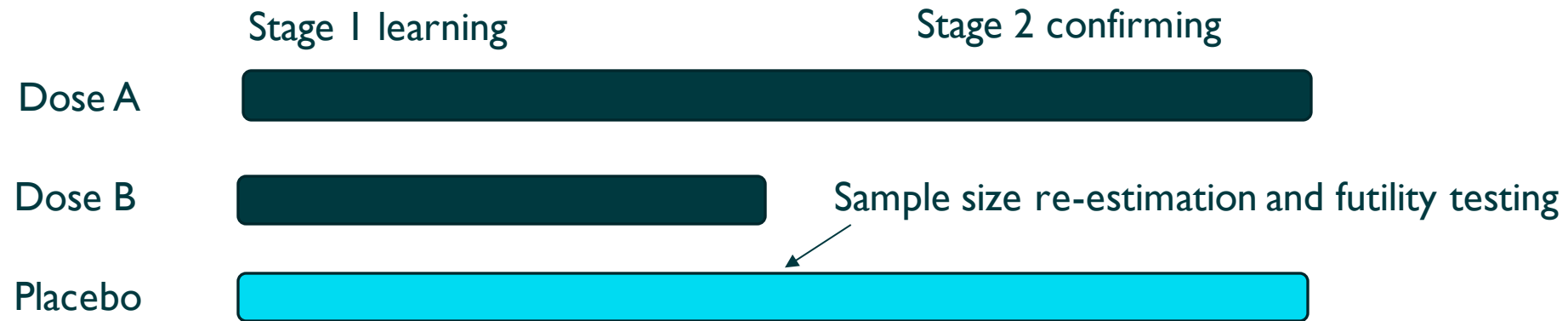
- Need of specific analytical methods
- Increased maximum sample size
- Logistical challenges to ensuring appropriate trial conduct and trial integrity
- Difference in results before and after adaptation



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Multiple Adaptations Example

- Let us suppose that trial is planned with two stages,
- First stage with two doses and placebo, second stage with selection of one of the dose and placebo
- Data will be combined for selected dose and placebo from stage 1 and stage 2
- Sample size is also planned to be re-estimated at completion of stage 1



Statistical Considerations

- Bias added to treatment estimates
 - Selection of treatment and combining data
 - Simulations can be run to quantify this bias
- Sample Size
 - n_1 for stage 1 to ensure that desired dose is selected
 - n_2 for stage 2 to ensure the trial has sufficient power

Statistical Considerations

- Type I error inflation
 - Early rejection at interim analysis (Rejection of doses)
 - Combining data from two stages
 - Multiple Hypothesis testing

Handling of Type I error Inflation

- Bonferroni Method for stage 1
 - Final hypothesis at α/m ; m is number of hypothesis at start of trial
 - Most conservative approach
 - Sample size re-estimation is not allowed
 - Well understood, straight forward and easy to implement

Handling of Type I error Inflation

- Bonferroni with closure principle at stage 1
 - For our case there are 2 hypothesis H1 and H2; hypothesis will be rejected if intersection hypothesis H12: $H1 \cap H2$ is rejected
 - $p1$ and $p2$ are p-values for H1 and H2,
 - $p12$ p-value for $H1 \cap H2 = 2\min(p1, p2)$
 - $p1 \leq \alpha$, and $p12 \leq \alpha$ then reject H1

Handling of Type I error Inflation

- Bonferroni with closure principle at stage 2 if Dose 2 is dropped
 - q_1 is p-value for H_1 at stage 2
 - $C(p_1, q_1)$ will be a combined p-value for testing H_1 at stage 2
- Bonferroni with closure principle at stage 2 with both doses
 - q_1, q_2, q_{12} are p-value for H_1, H_2 and H_{12} at stage 2
 - Combined p-value would need to be calculated for all three hypothesis to conclude

Handling of Type I error Inflation

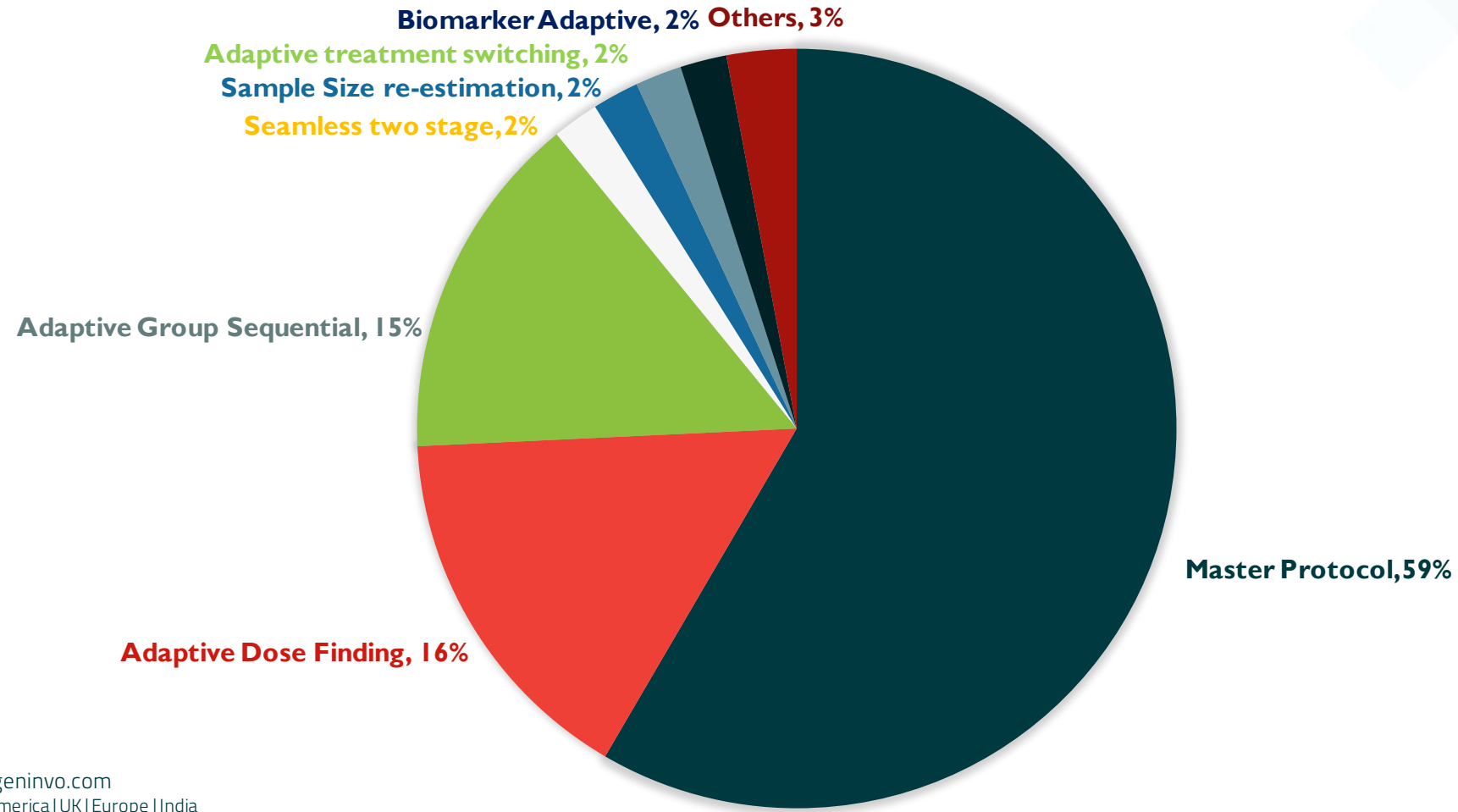
- Methods of combining p-values
 - Fisher's product: $C(p_1, p_2) = p_1 p_2$ (as shown by Bauer and Kohne 1994)
 - Inverse normal method
 - $C(p_1, p_2) = \sqrt{w} \Phi^{-1}(1-p_1) + \sqrt{1-w} \Phi^{-1}(1-p_2) \sim N(0,1)$
 - n_1 = Sample size from Stage 1
 - n_2 = Sample size from Stage 2
 - $w = n_1/(n_1+n_2)$

Sample Size

- 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)

Adaptive Design Trials in past

Adaptive Design trials conducted between 1998 to 2020



References

- Wang S, Ma P, Lei Q, Fang Y, Huang H, et al. (2021) Evolution of global clinical trials with adaptive design. Clin Res Trials 7: doi: 10.15761/CRT.1000353
- USFDA (2019), Adaptive Designs for Clinical Trials of Drugs and Biologics, Guidance for Industry
- Bauer, P and K Kohne, 1994, Evaluation of Experiments with Adaptive Interim Analyses. Biometrics, 50(4):1029–1041
- USFDA (2017), Multiple Endpoints in Clinical Trials, Guidance for Industry



Ideas
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Thank You!

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