

# Use of Simulations for Sample Size Calculation in a Dose-Ranging Study

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## Introduction

- Sample size calculations for a dose-ranging study investigating multiple doses of an active treatment against placebo. Interested in selecting the optimal dose for safety, tolerability and efficacy and estimating the dose response curve.
- Sample size calculations across a multi-arm parallel group design like this are often overestimated by standard methods. Sample size is also affected by trial design.
- Simulated data was used to investigate sample size requirements under different trial design options. Estimated power from these simulations was then used to select the most efficient design.

## Trial Designs

- Would a design with a higher number of treatment arms but fewer subjects in each perform better as intervals between the observed points on the dose response curve would be shorter? Or would a design with fewer treatment arms but more subjects in each perform better since better precision would be achieved at each observed point?
- Effects of reducing allocation to the lower dose groups was also investigated and cut-off points for a possible interim analysis were compared.

## Initial Assumptions

### Assumptions

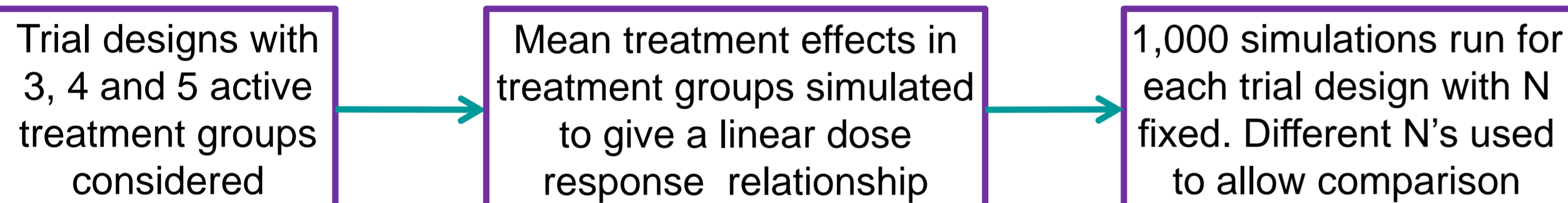
- Endpoint: mean change from baseline
  - 1 in placebo group
  - 2 in max dose group
- SD of 2.5 within each dosing group
- Linear dose/response relationship

Linear dose response relationship was a likely candidate for the true relationship between the treatment and the endpoint. Figure 1 shows other candidate relationships



Figure 1

## Method



Treatment effects  $y_i$  in each treatment group were derived to be the contrast between the estimated change from baseline in the  $i^{\text{th}}$  treatment group  $\theta_i$  compared to placebo group  $\theta_1$ :

$$y_i = \theta_i - \theta_1 \text{ for } i=(2, \dots, j)$$

Empirical power was estimated as the number of simulations out of 1,000 that detected the treatment effect with statistical significance in the maximum or second to maximum active treatment group,  $y_j, y_{j-1}$ .

## Results

### Linear Dose Response

- Optimal trial design had three active treatment groups. Empirical power vs sample size is shown in Figure 2.
- When the allocation rate was decreased to the lower treatment groups the difference between the trial designs was less apparent.

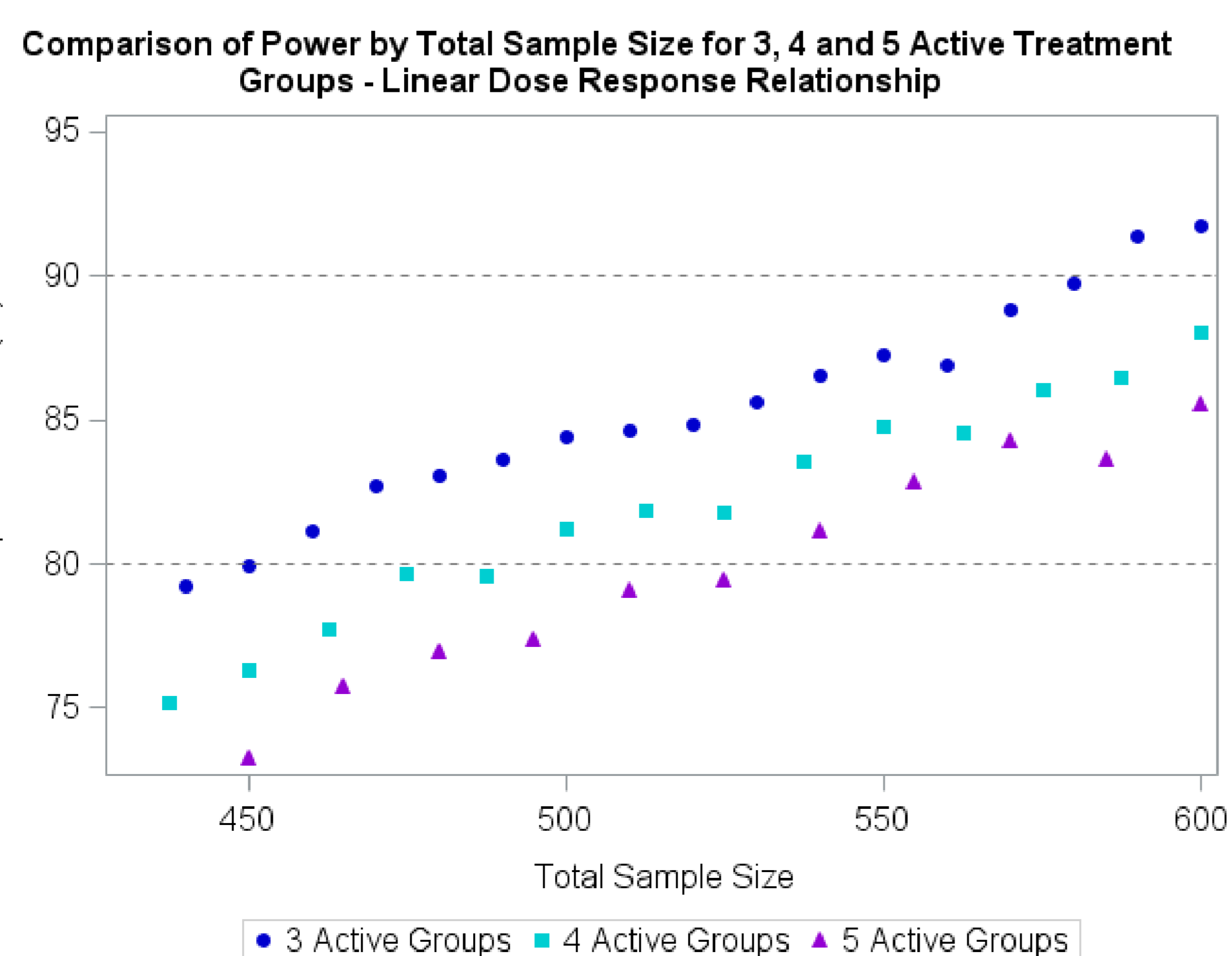


Figure 2

## Results Continued

### Non-Linear Dose Response

- Optimal trial design changed to one with five active treatment groups. Empirical power vs sample size is shown in Figure 3.
- Model fit was the best in the simulations with four and five active treatment groups.

Comparison of Power by Total Sample Size for 3, 4 and 5 Active Treatment Groups - Non Linear Dose Response Relationship

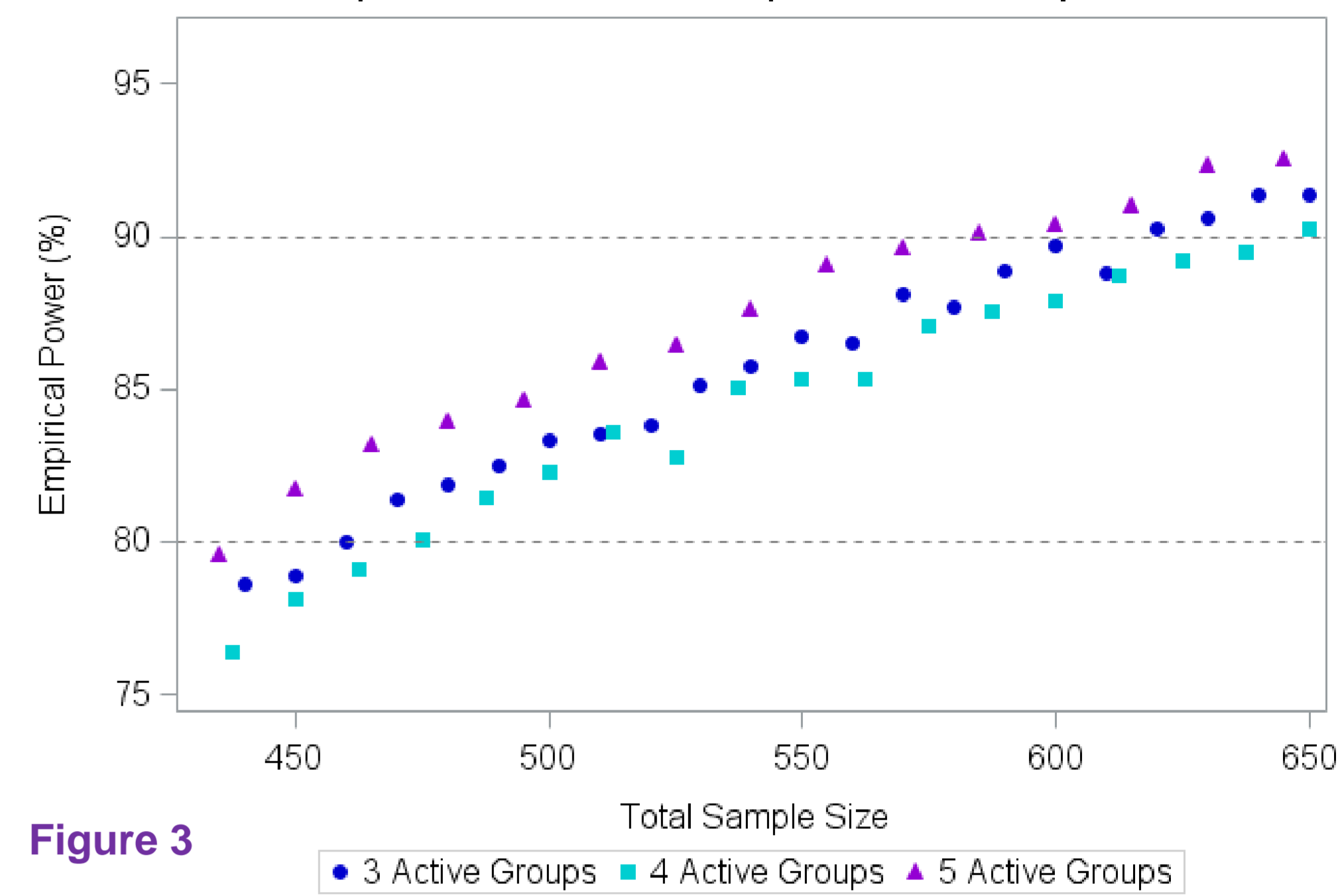
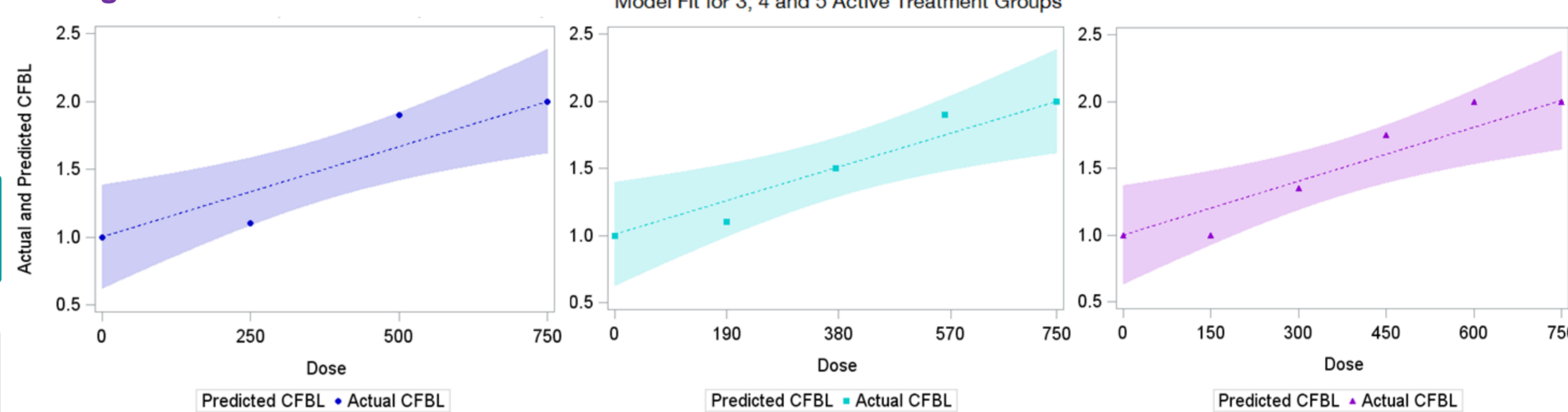


Figure 3

### Figure 4



## Interim Analysis

- What is the optimal choice for mean change from baseline in the first half of the study? What is the probability of a significant result?

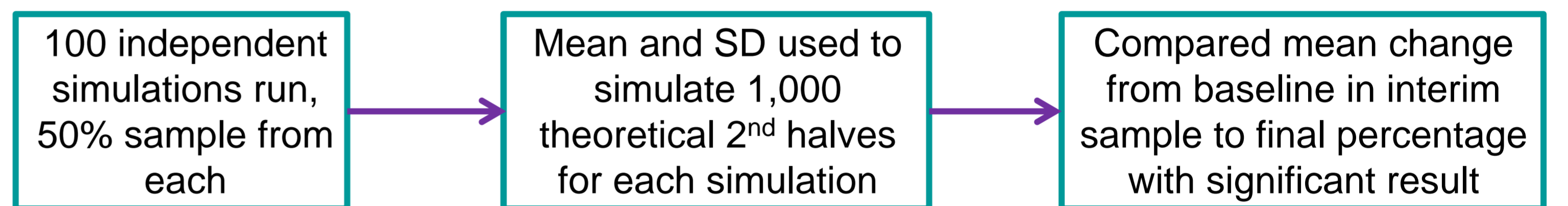
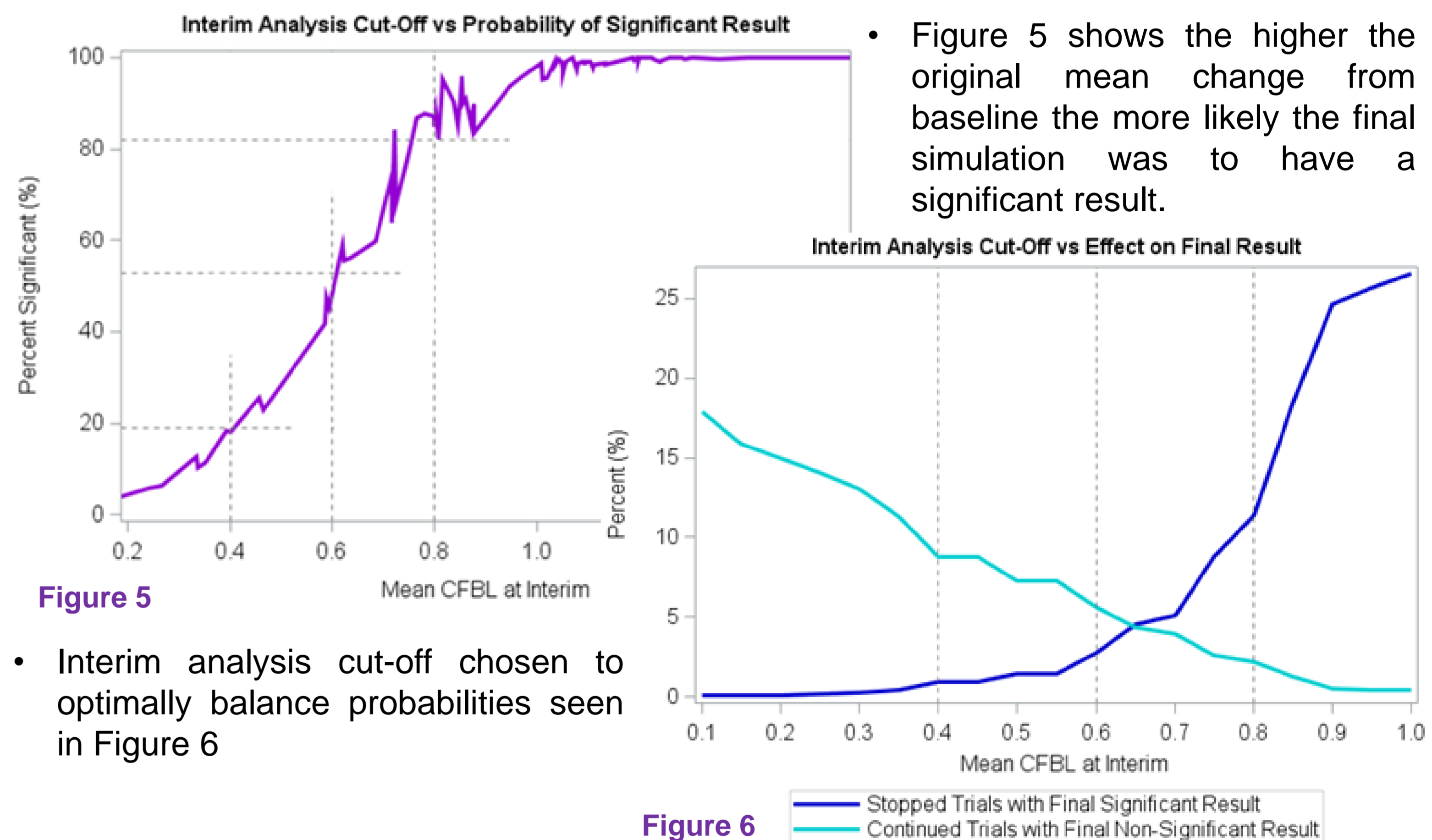


Figure 5 shows the higher the original mean change from baseline the more likely the final simulation was to have a significant result.



- Interim analysis cut-off chosen to optimally balance probabilities seen in Figure 6

Figure 6

## Conclusion

- The total number of subjects required was similar across all trial designs. Reducing allocation to lower active treatment groups reduced total number of subjects required while maintaining similar power.
- Overall simulations were sensitive to changes in the assumptions with the result prone to vary for differing dose response relationships and high number of simulations required to smooth variations. Designs with 4 and 5 groups were more robust to variation in the assumed shape of the data.

## References

Christian Holm Hansen, Pamela Warner, Richard A Parker, Brian R Walker, Hilary OD Critchley and Christopher J Weir; Development of a Bayesian response-adaptive trial design for the Dexamethasone for Excessive Menstruation study; SMMR 2017 Vol. 26(6)