Frequentist Response Adaptive Randomisation

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Joint work with Prof. Thomas Lumey & Associate Prof. Alain Vandal

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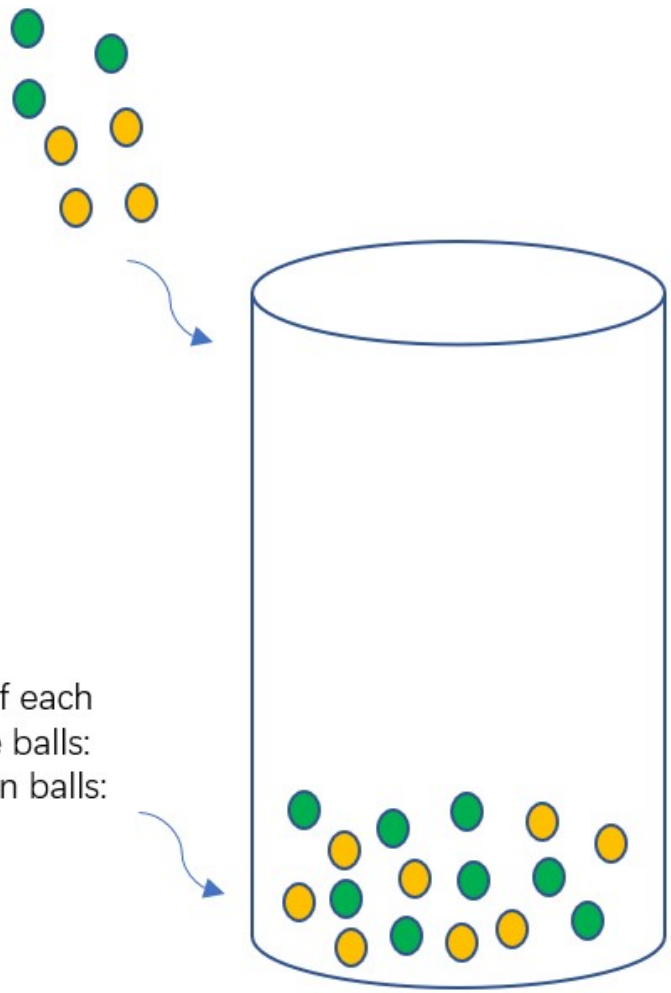
Outline

Randomized Play-the-Winner Rule



If response to treatment A (orange) is a success, then add ß orange balls and an additional α green balls to the urn.

If response to treatment A (orange) is a failure, then add ß green balls and an additional α orange balls to the urn.

Start with u balls of each treatment. Orange balls: Treatment A; Green balls: Treatment B.

RPW(u, α, ß)

Research Questions

- Analyse the impact of response-adaptive randomisation on treatment uptake in the population (as well as the trial).
- Evaluate response-adaptive randomisation methods from Frequentist perspectives compared to group sequential design and equal randomisation.
- Assess the effects of delayed responses and multiple arms.

Doubly Adaptive Biased Coin Design

'Doubly' means there are two parameters, the current allocation ratio and the current estimate of the desired allocation ratio;

'Adaptive' means that the unknown parameters are sequentially updated with their corresponding maximum likelihood estimators;

'Biased Coin' indicates the allocation probability to each group is seldom equal to $\frac{1}{2}$ during the process.

- Four or more patients will be allocated to two treatment groups equally;
- The newly enrolled t^{th} patient will be assigned to treatment A with probability $f\left(\frac{N_{A,(t-1)}}{n_{(t-1)}}, \rho(\hat{p}_{A,t-1}, \hat{p}_{B,t-1})\right)$.

Doubly Adaptive Biased Coin Design

Hu & Zhang 's Allocation Function

$$f\left(\frac{N_A,(t-1)}{n_{(t-1)}},\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1})\right)=$$

$$\frac{\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1})\left(\frac{\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1})}{\frac{N_{A,(t-1)}}{n_{(t-1)}}}\right)^{\gamma}}{\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1})\left(\frac{\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1})}{\frac{N_{A,(t-1)}}{n_{(t-1)}}}\right)^{\gamma}+(1-\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1}))\left(\frac{1-\rho(\hat{p}_{A,t-1},\hat{p}_{B,t-1})}{1-\frac{N_{A,(t-1)}}{n_{(t-1)}}}\right)^{\gamma}}.$$

The generalisation of Hu & Zhang's allocation function to K arms is given as:

$$\phi_{tk}=\frac{\hat{\rho}_{k,t-1}{}^{*}\left(\frac{\hat{\rho}^{*}_{k,t-1}}{\frac{N_{k,t-1}}{t-1}}\right)^{\gamma}}{\sum_{i=1}^{K}\hat{\rho}_{i,t-1}{}^{*}\left(\frac{\hat{\rho}^{*}_{i,t-1}}{\frac{N_{i,t-1}}{t-1}}\right)^{\gamma}}.$$

Doubly Adaptive Biased Coin Design

Neyman Allocation

For fixed variance of the test statistic under an alternative hypothesis, what allocation minimizes the total sample size?

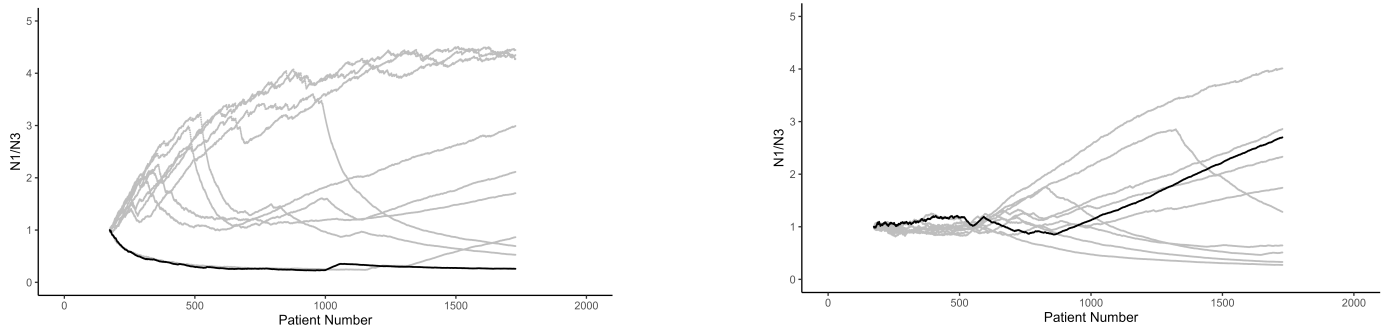
$$\rho_A = \frac{\sqrt{p_A q_A}}{\sqrt{p_A q_A} + \sqrt{p_B q_B}}$$

RSIHR Allocation

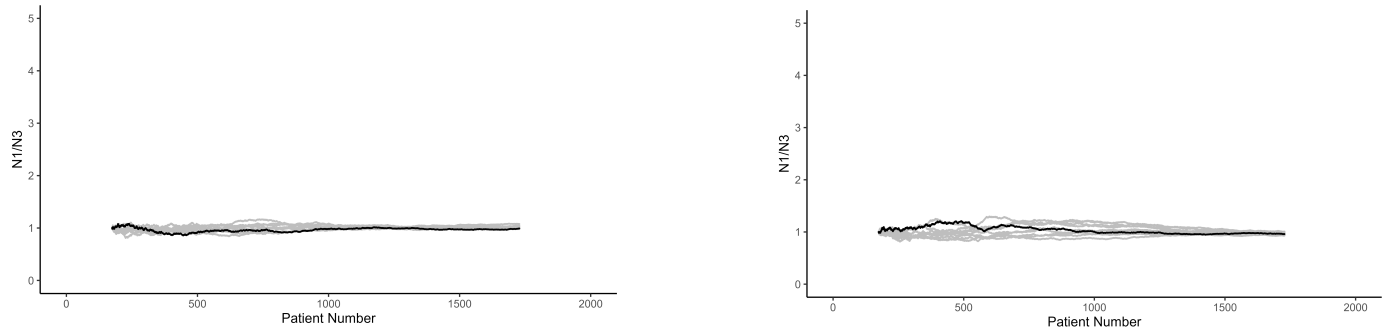
or fixed variance of the test statistic under an alternative hypothesis, what allocation minimizes the expected number of treatment failures?

$$\rho_A = \frac{\sqrt{p_A}}{\sqrt{p_A} + \sqrt{p_B}}$$

Results - Three Arms



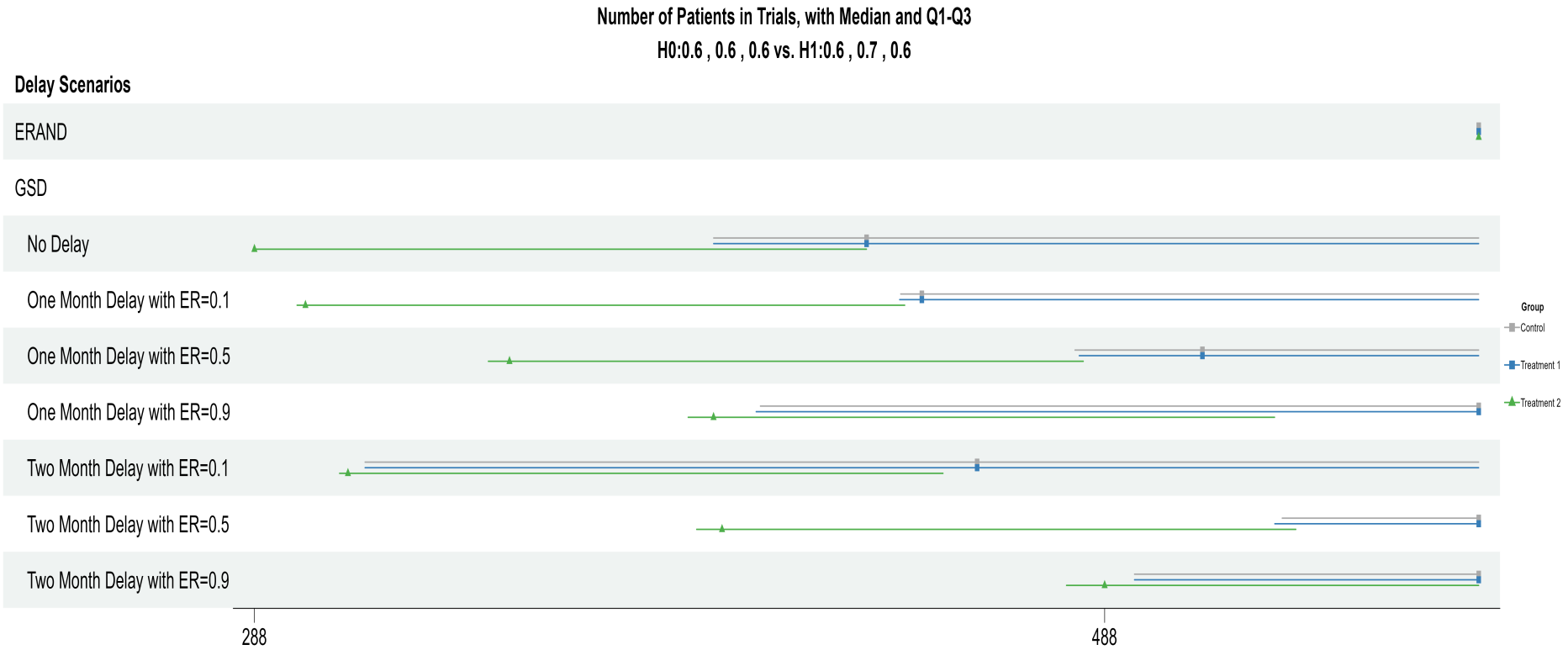
(a) Doubly adaptive biased coin design to maximise power
No Delay (Left) Two Month Delay with Enroll Rate 0.9 (Right)



(b) Doubly adaptive biased coin design to minimise variance
No Delay (Left) Two Month Delay with Enroll Rate 0.9 (Right)

Figure: Change of N1/N3 Over Time After Equal Randomisation of Maximal Power and Minimal Variance of Doubly Adaptive Biased Coin Design Using Neyman Allocation for H0: 0.6, 0.6, 0.6 vs. H1: 0.6, 0.7, 0.6

Results - Three Arms, In the Trial

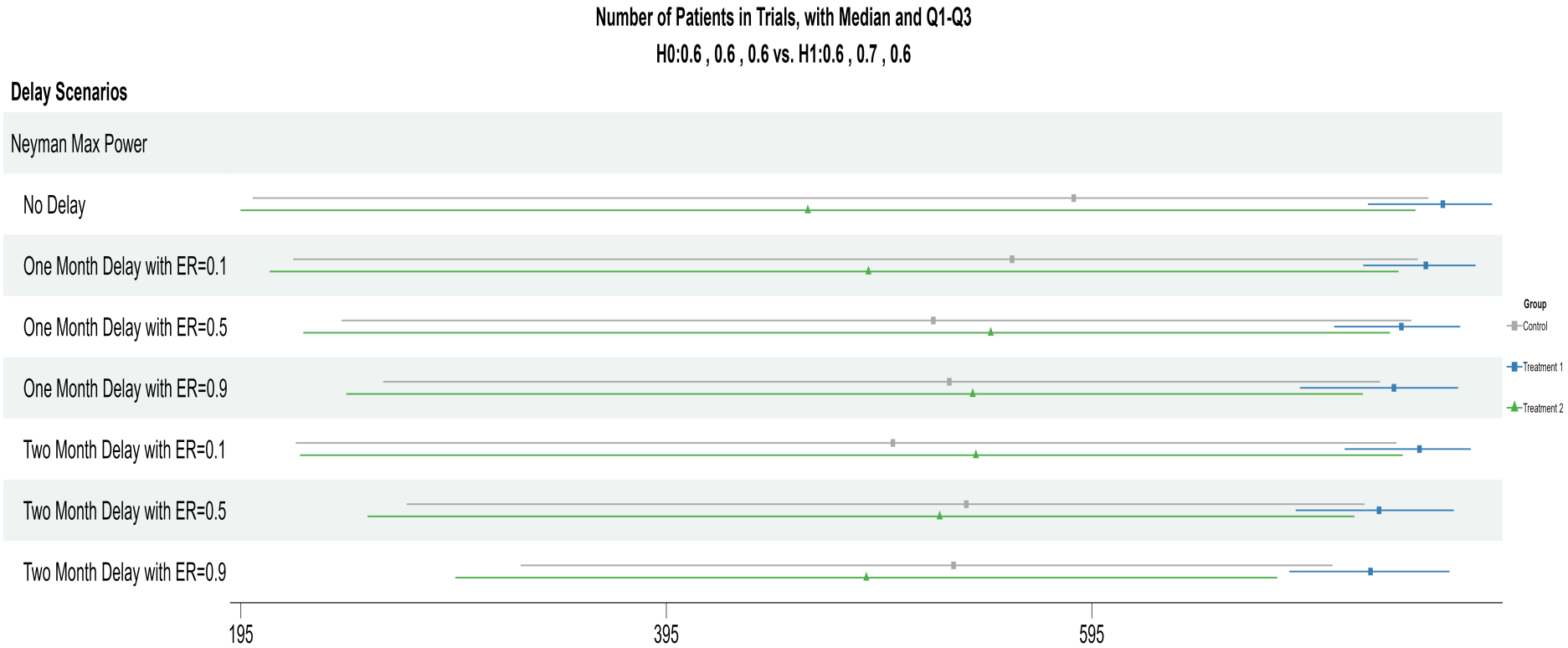


ERAND:Equal Randomisation; GSD:Group Sequential Design;

ER: Enrollment Rate

Sample Size: 1728

Results - Three Arms, In the Trial



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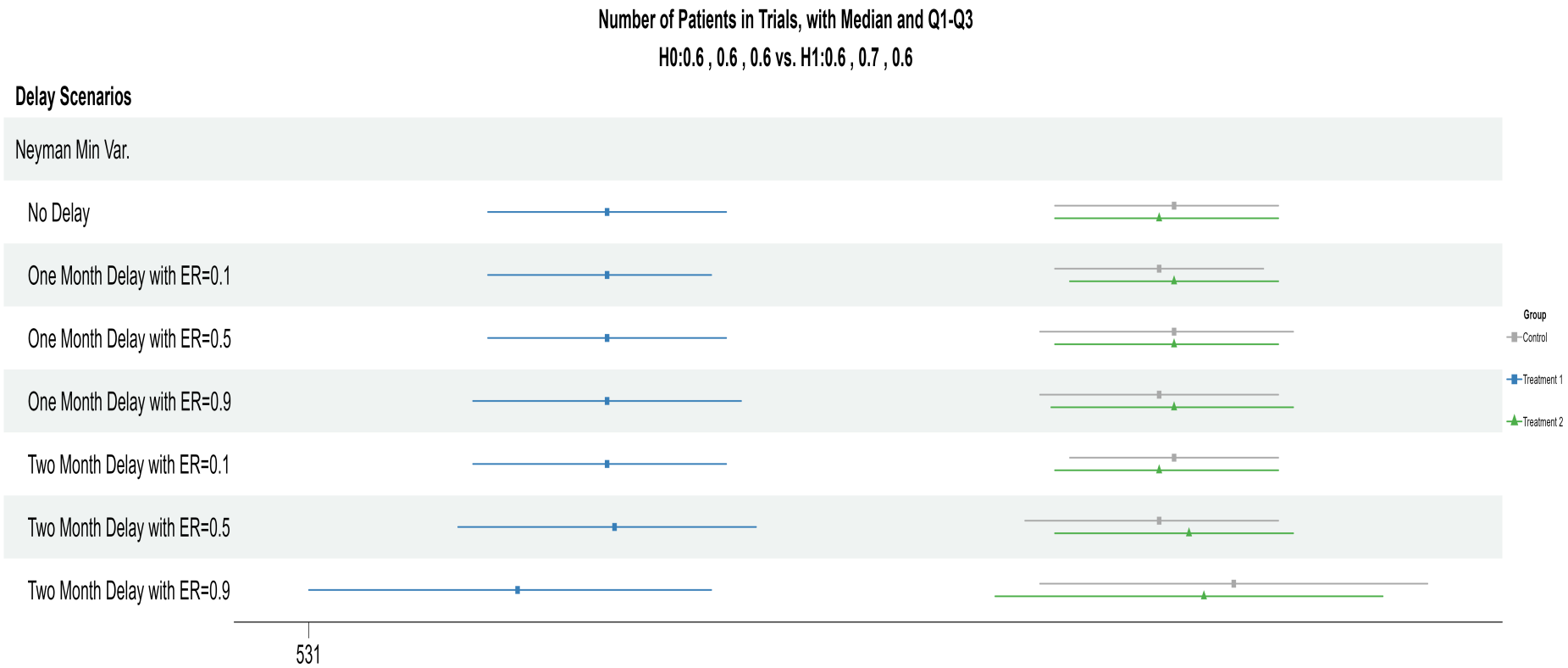

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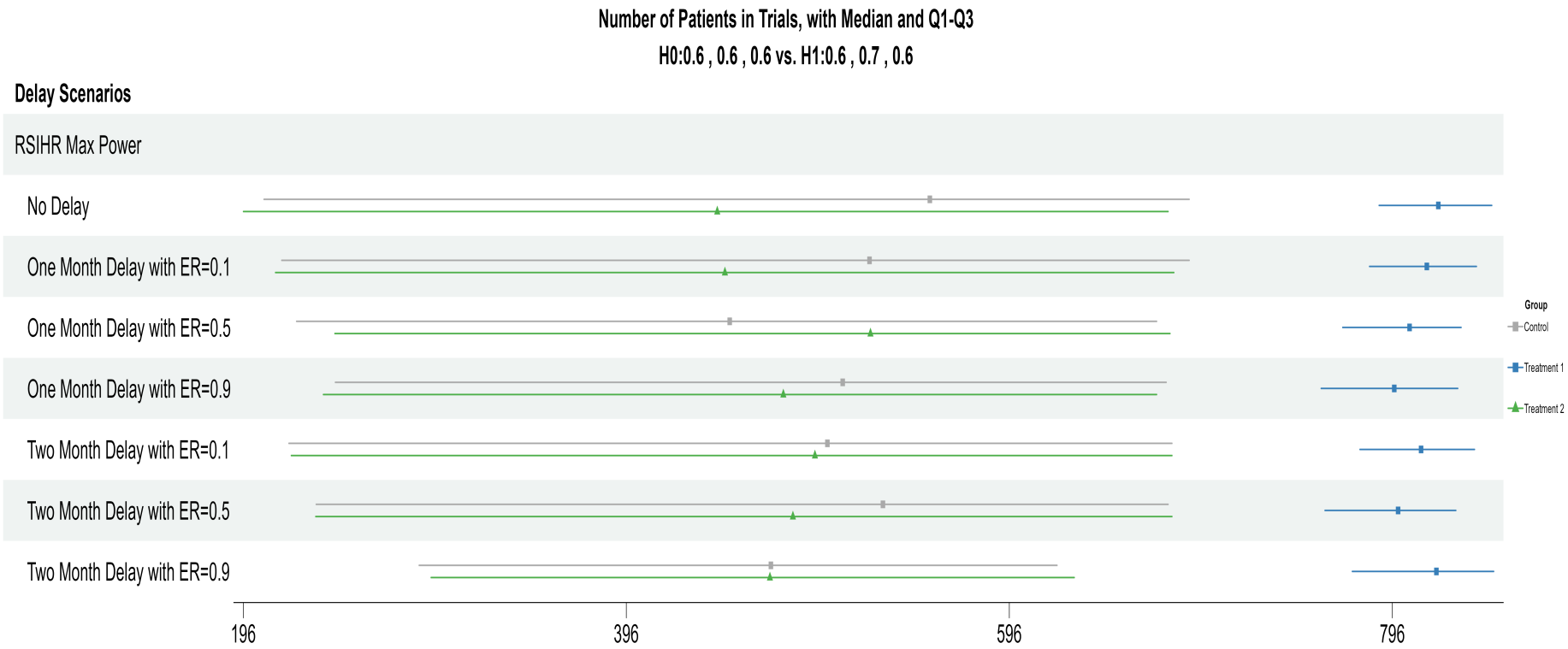

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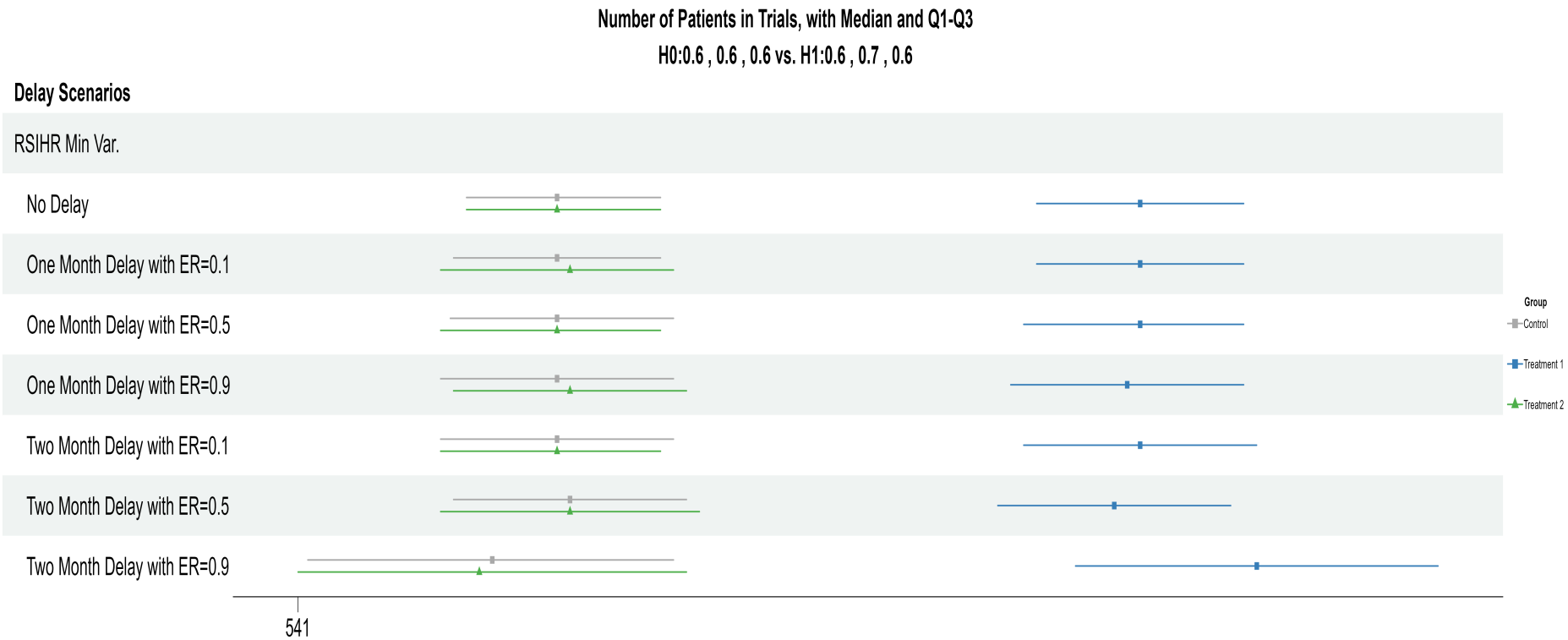

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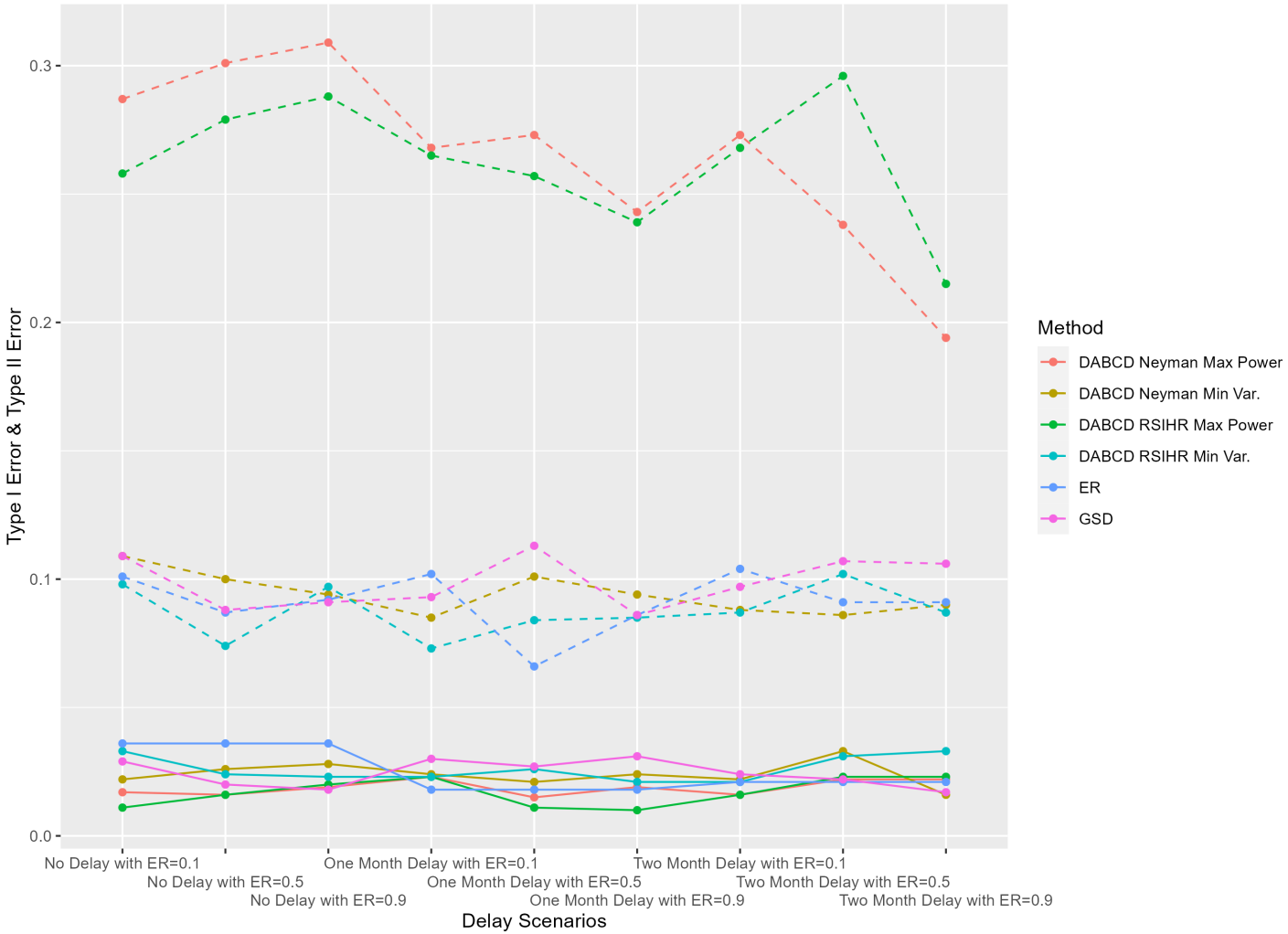
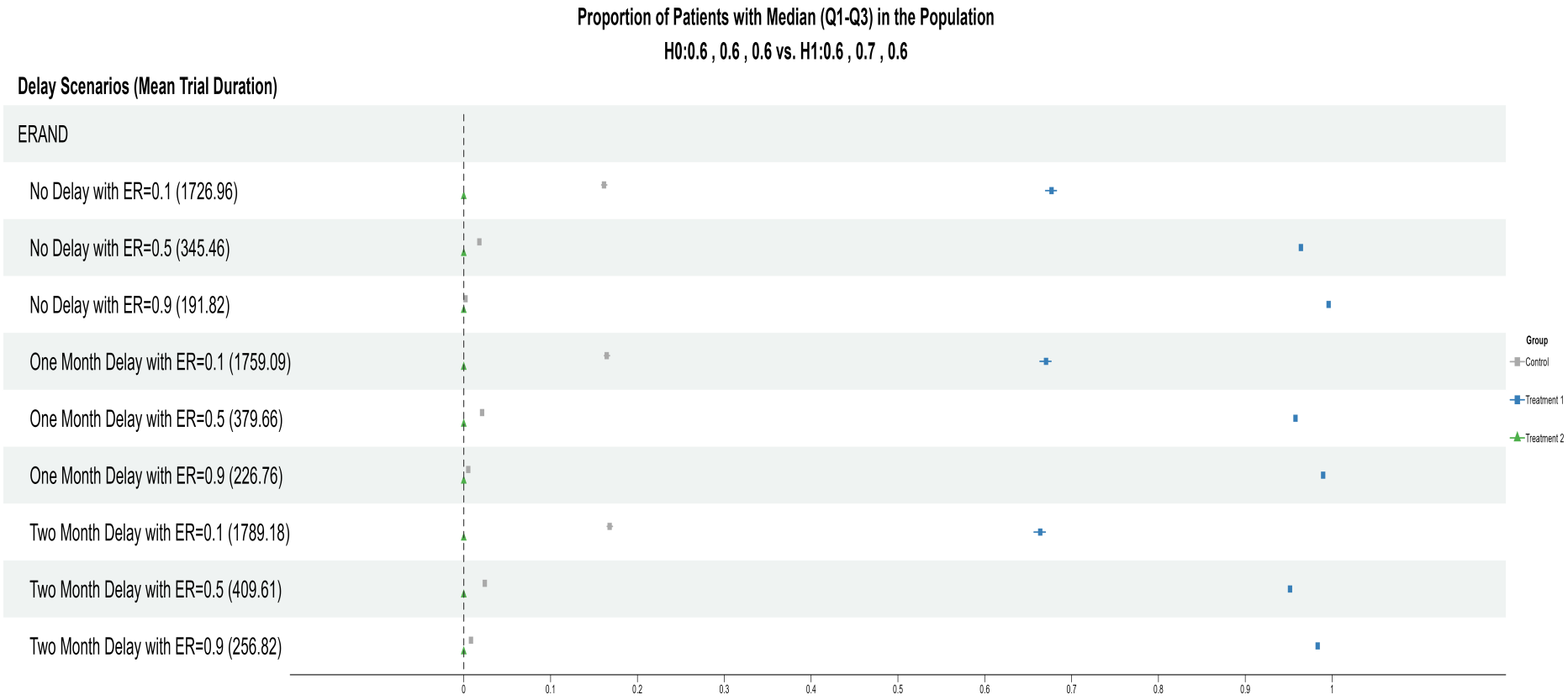


Note: Sampling error at 0.7 is 0.0284.

Figure: Line Plot of Type I and Type II Errors Based on Marginal Power and Overall Power for H0: 0.6, 0.6, 0.6 vs. H1: 0.6, 0.7, 0.6

Results - Three Arms, In the Population



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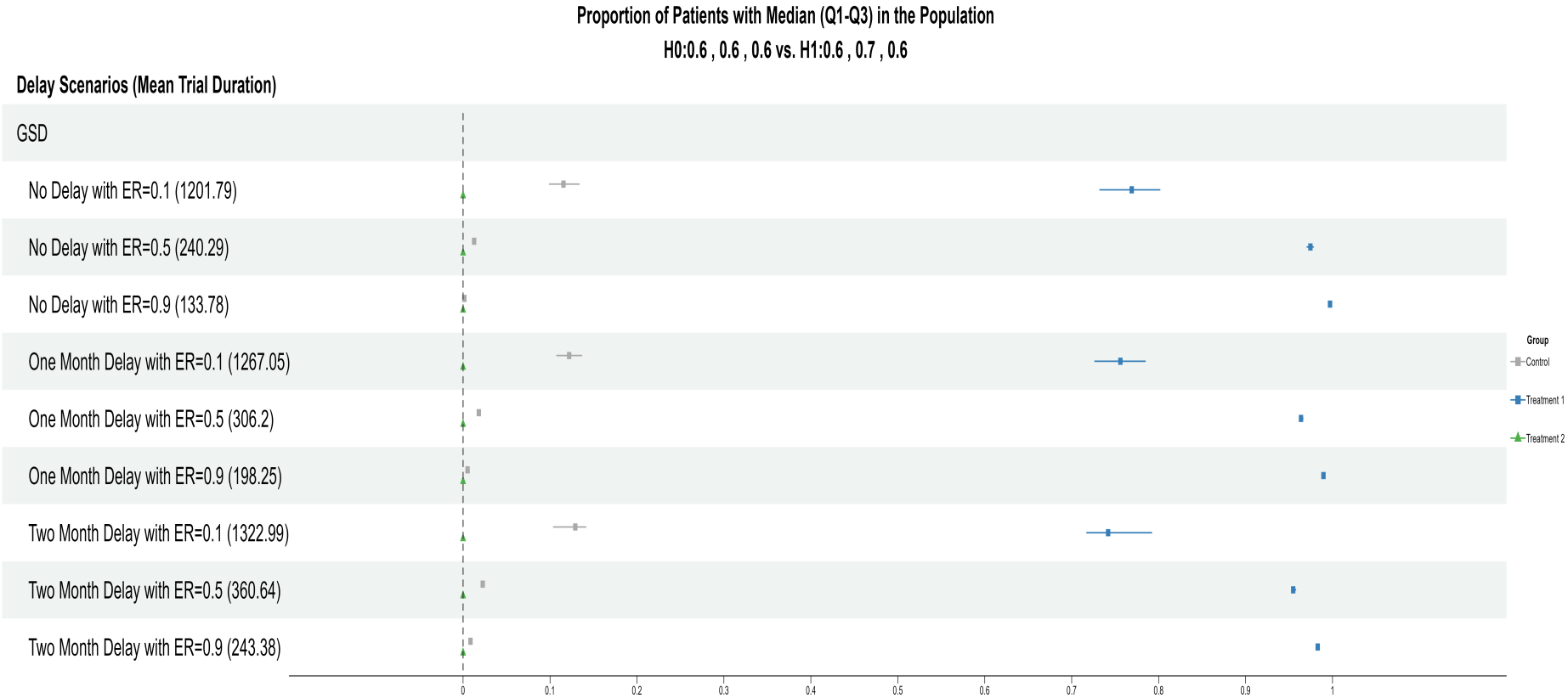

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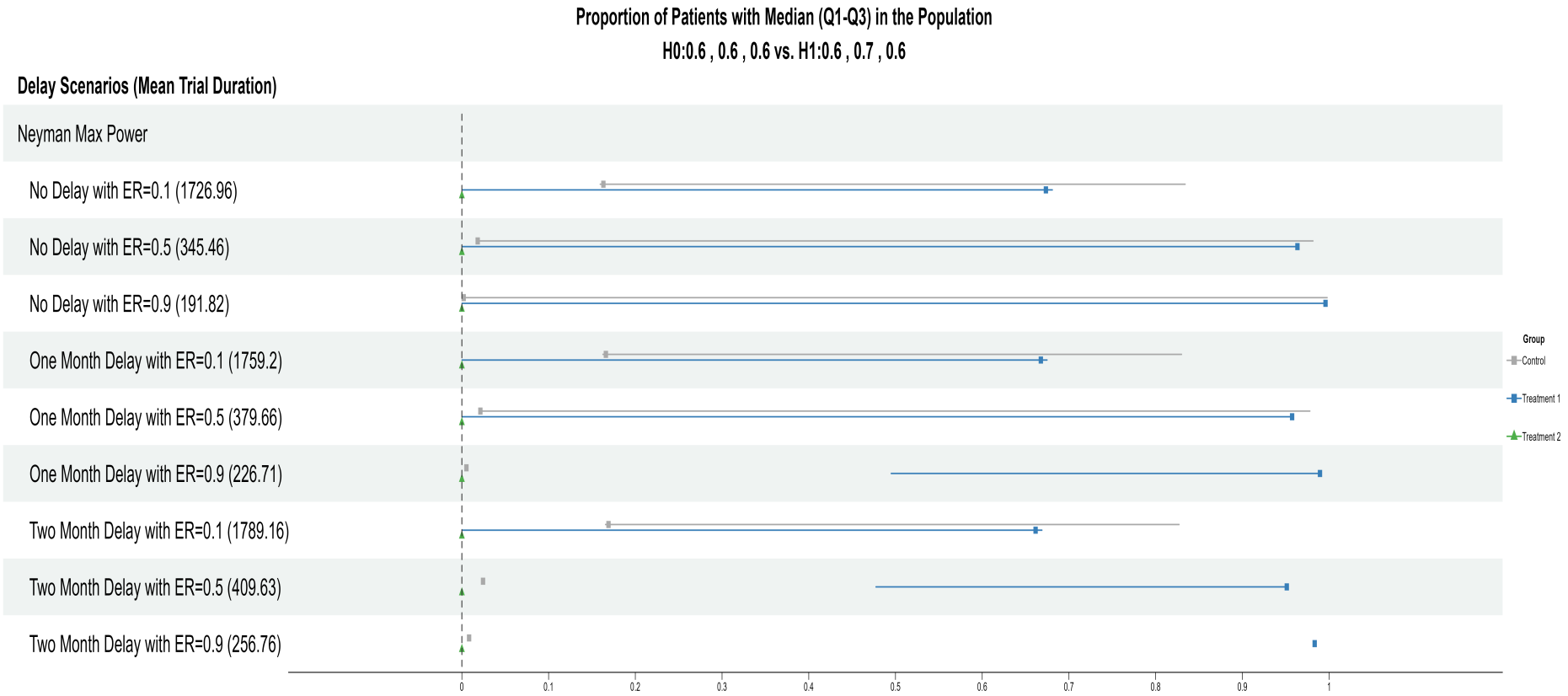

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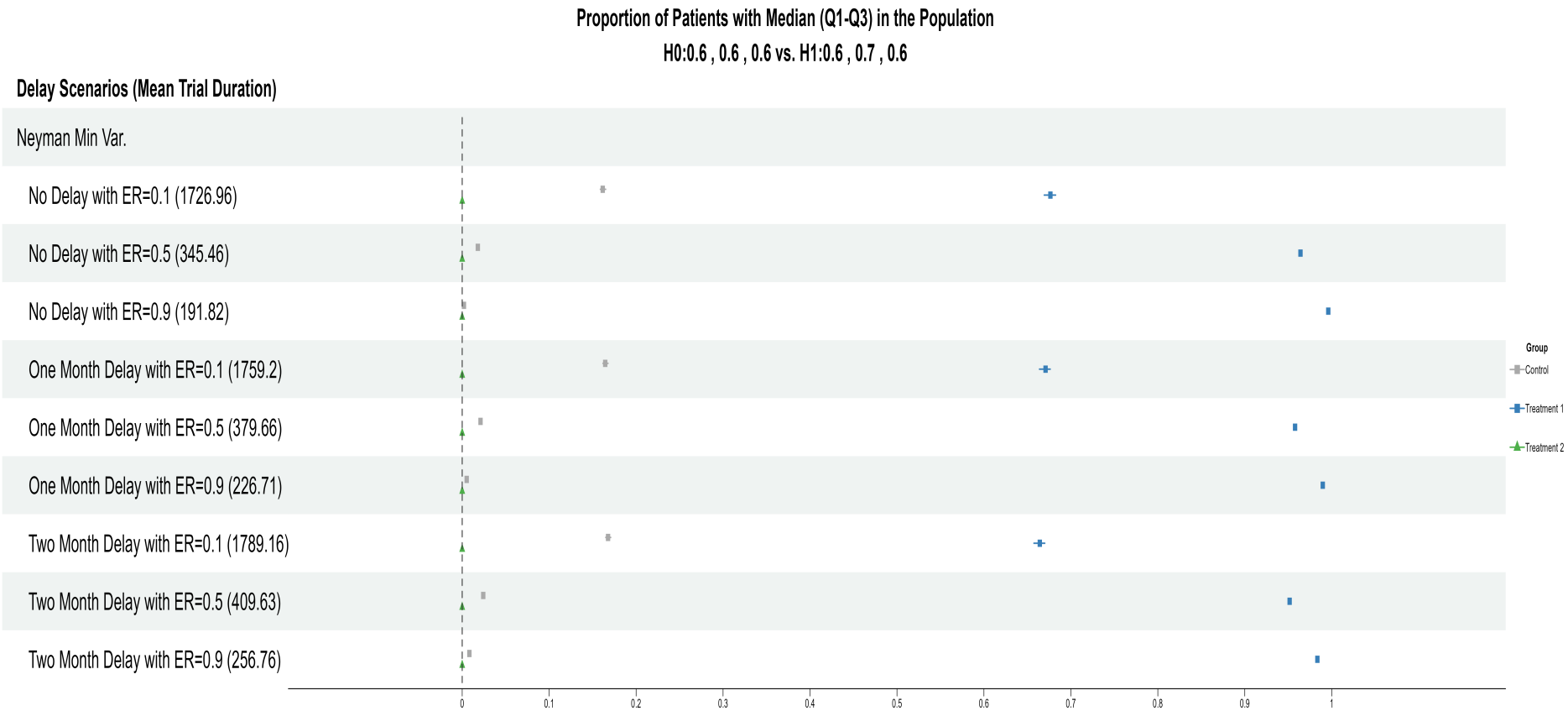

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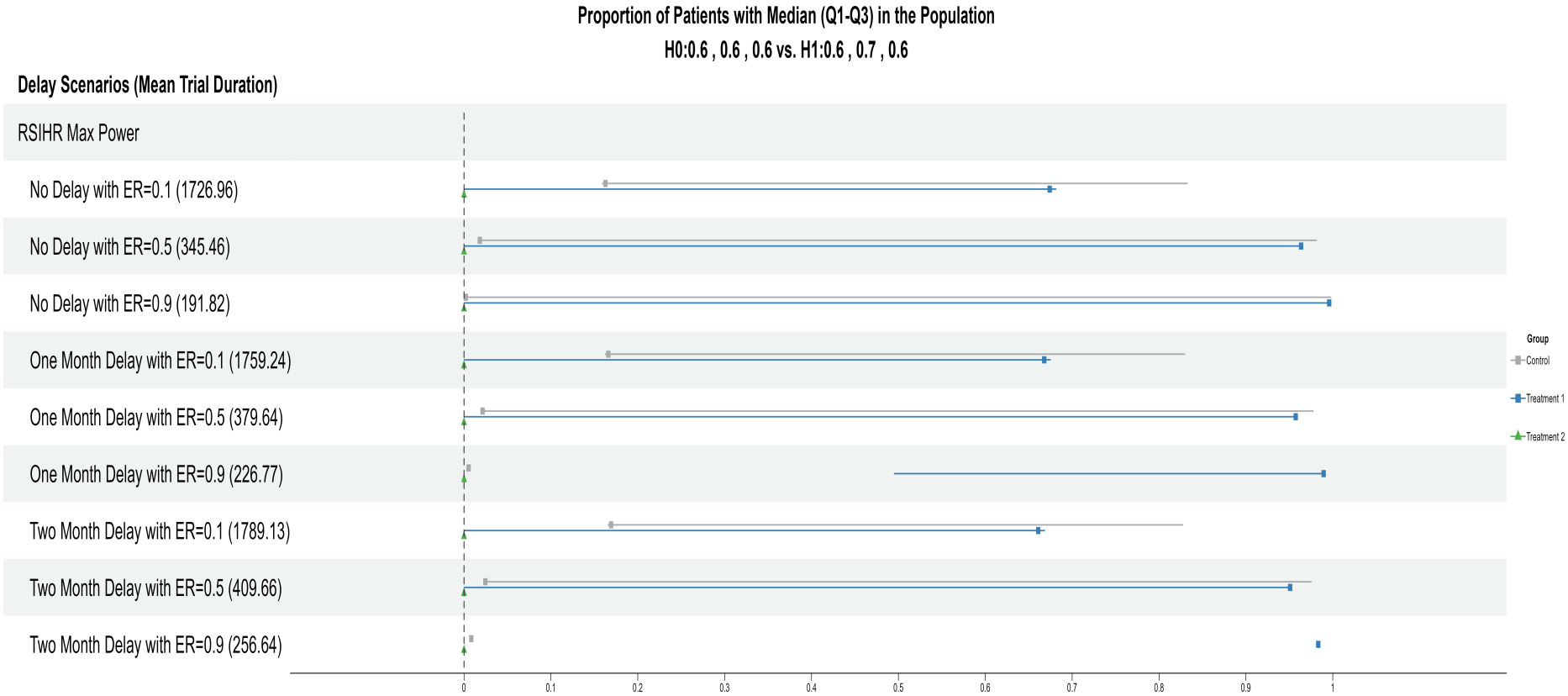

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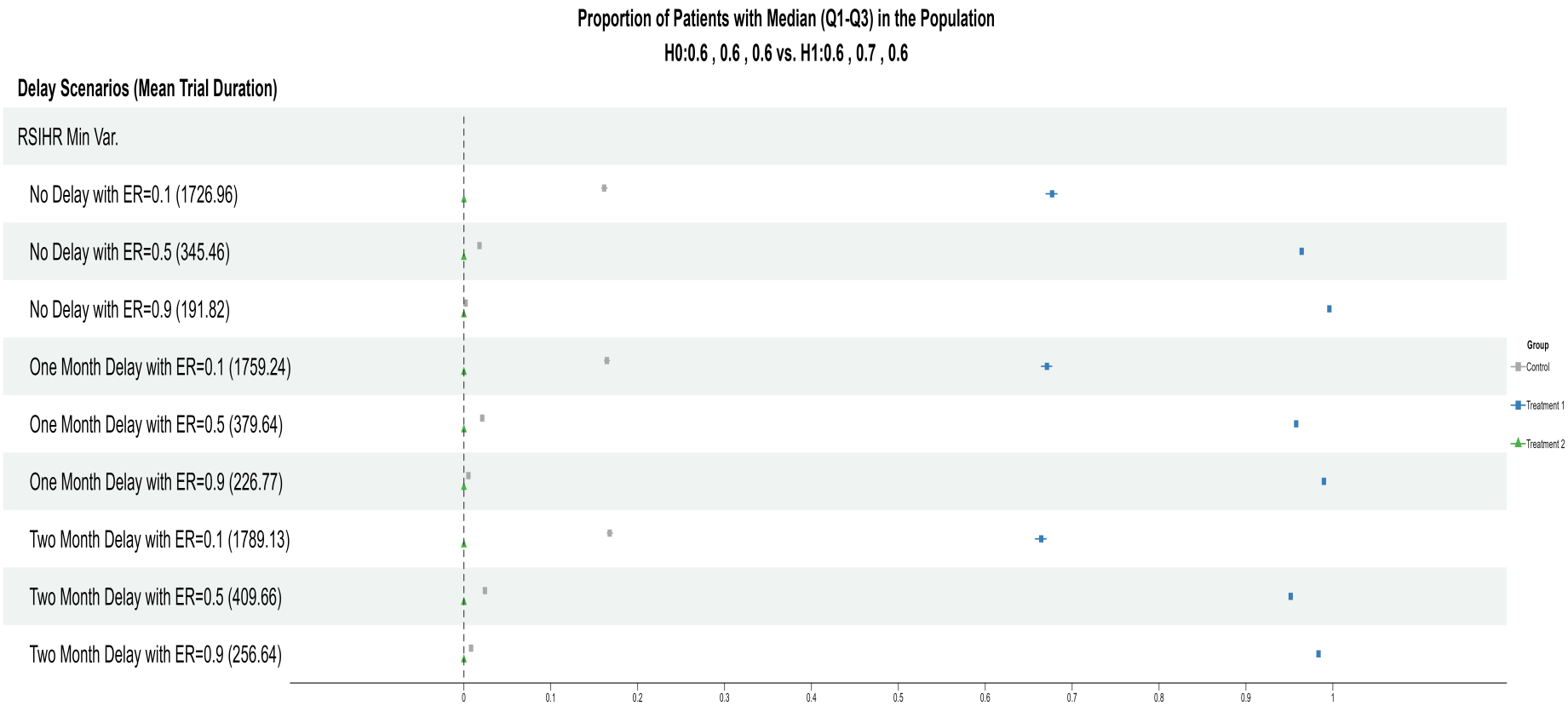

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Conclusion

- Power is impacted more using the doubly adaptive biased coin design with maximal power strategy than other methods.
- The proportions of patients in the population can take each treatment changes with the power of trials and duration of trials.
- As delay and enrollment rate increase, all the methods tend to be the same assigning patients in the population to different treatment groups as the marginal power and trial duration become close to each other.

Conclusion

- Doubly adaptive biased coin design with maximal power strategy is easier to assign more patients to one superior treatment in the trials but there is more variance assigning patients both in the trial and in the population compared to all the other designs.
- The unbalanced allocation results in the trials is small using the doubly adaptive biased coin design with minimal variance strategy, which leads to the similar results for treatment uptake in the population compared to equal randomisation and group sequential design.

Thank you!