

Dynamic Enrichment of Bayesian Small Sample, Sequential, Multiple Assignment Randomized Trial (snSMART) Design Using Natural History Data: A Case Study From Duchenne Muscular Dystrophy

Sidi Wang, Kelley M Kidwell, Satrajit Roychoudhury

Department of Biostatistics, University of Michigan

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Disclosures

- ▶ Sidi Wang: No disclosures

Background on snSMART

- ▶ Difficult to conduct RCTs with small sample size
- ▶ snSMART (small sample, sequential, multiple assignment, randomized trial) design ^[11] is a similar design to a classic SMART but with equal time length for both stages and a focus on identifying **the superior first-stage treatment**
- ▶ Progress in statistical methods for analyzing data from various snSMART designs ^[1, 2, 3, 4, 5, 12, 13].

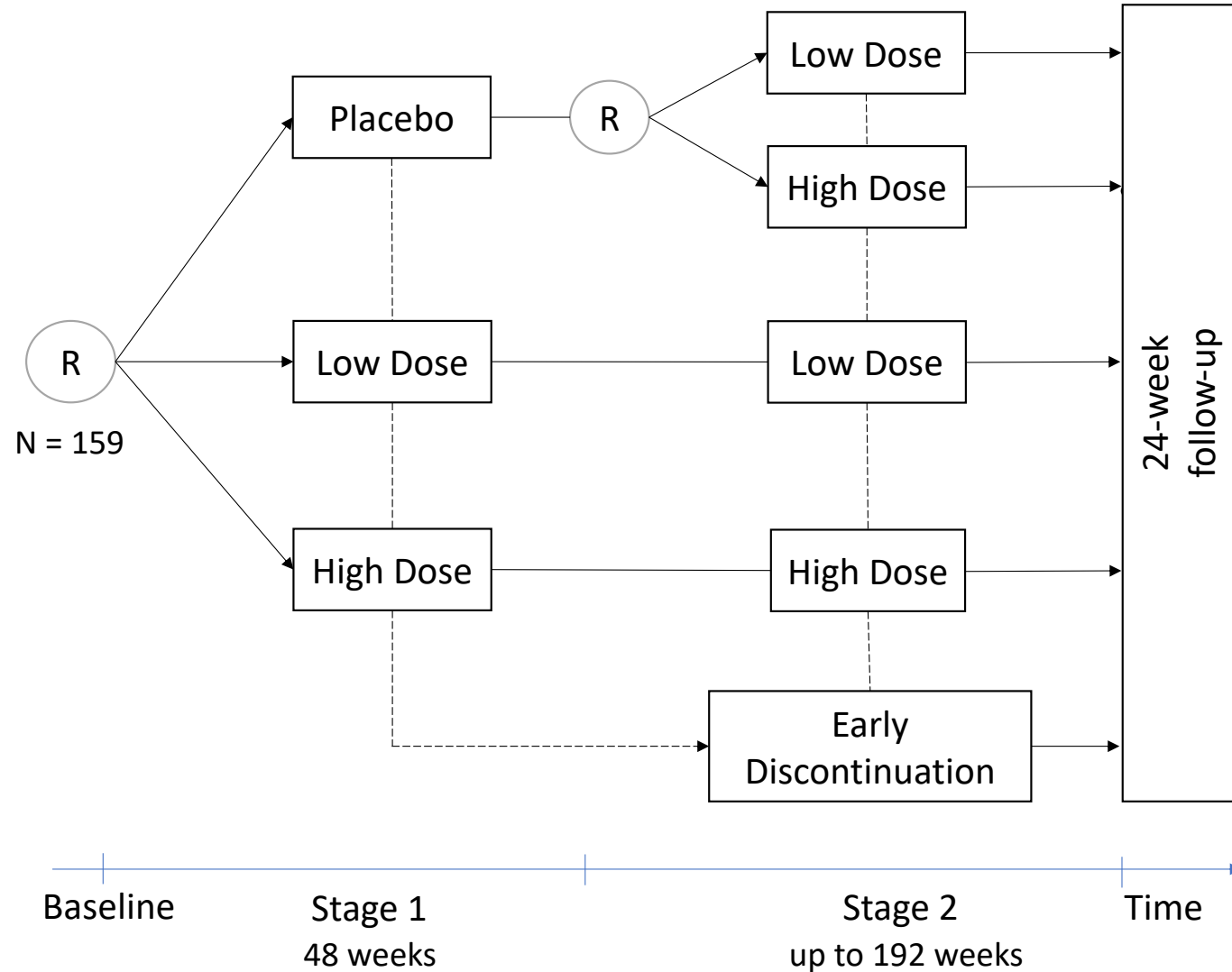
Background on External Control Data Integration

- ▶ Integrating external control data in clinical trials is important to improve efficiency and precision of trials
- ▶ Existing methods: bias model, test-then-pool approach, propensity score methods, power prior distributions, commensurate priors, meta-analytic methods [6, 7, 8, 9, 10].

Motivation

- ▶ Drug developers and regulators interested in incorporating external control data into clinical trials to **reduce the number of participants** in the control arm
- ▶ FDA recognizes well-designed **natural history studies** as a potential source of external control data in rare disease clinical trials
- ▶ Significant **unmet needs** for effective treatments for many rare diseases, e.g., Duchenne muscular dystrophy (DMD)
- ▶ None of the existing snSMART designs formally incorporate external control data

Motivating Example: DMD SPITFIRE TRIAL NCT03039686



Motivating Example

- ▶ **Primary endpoint:**

 - North Star Ambulatory Assessment (NSAA) total score

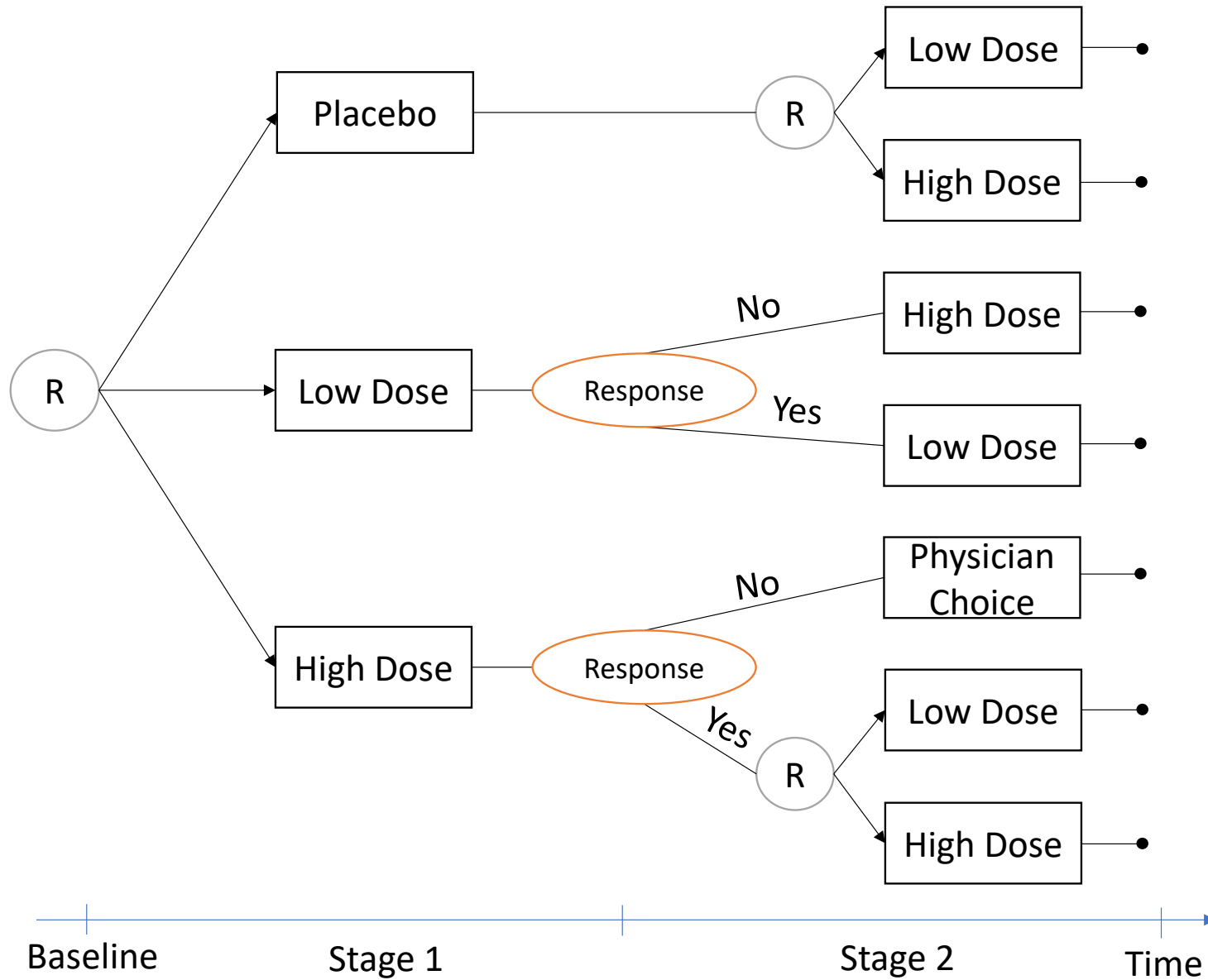
- ▶ **Secondary outcome:**

 - 6-Minute Walk Distance (6MWD)

- ▶ **Issues:**

1. Only the participants in the control group were rerandomized in stage 2. Potential issues with **recruitment and retention**
2. Current approach **ignores the second stage** data in the efficacy analysis

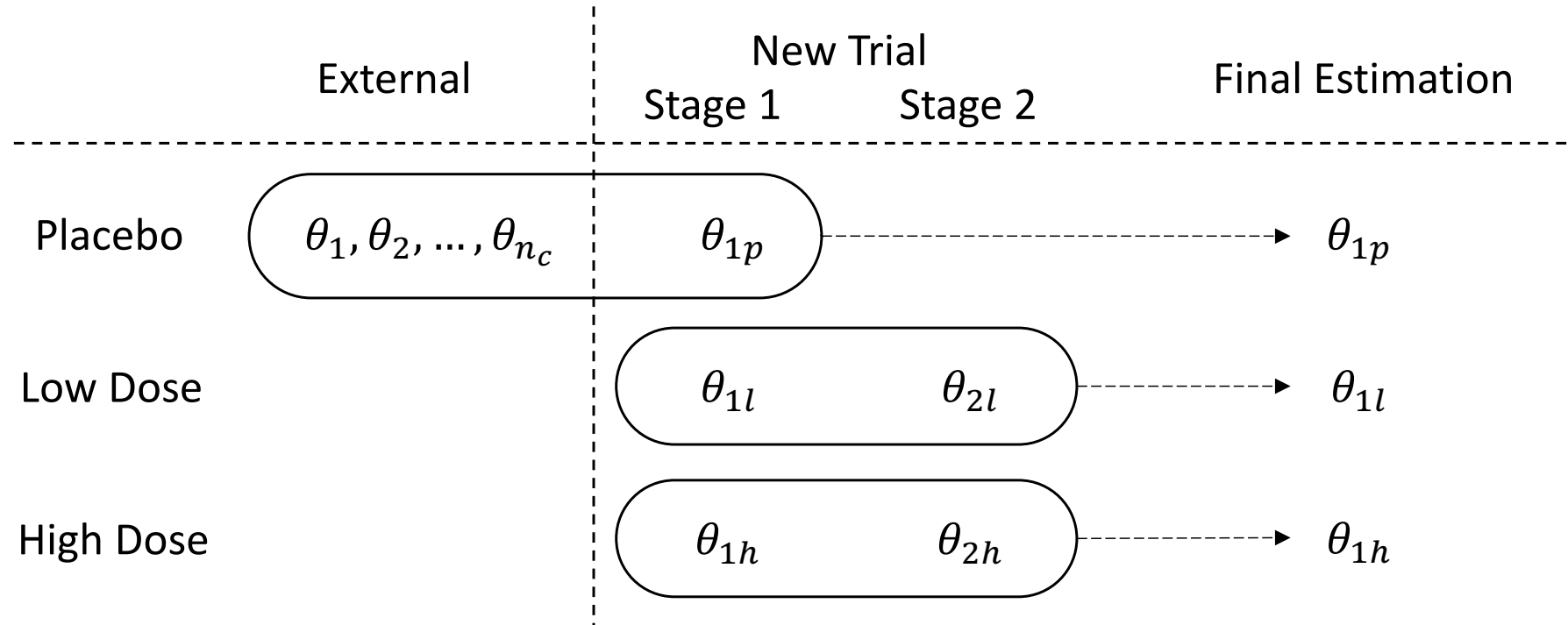
Proposed Trial Design: snSMART



MAC-snSMART Method

External Control	New Trial
i : External control data, takes value 1, 2, ..., n_c	j : Trial stage, takes value 1 or 2
Y_i : Observed mean placebo effect in external control data i	k : Treatment, takes value p (placebo), l (low dose), or h (high dose)
θ_i : Expected mean placebo effect in external control data i	Y_{jk} : Observed mean treatment effects for stage j and treatment k
	θ_{jk} : Expected treatment effects for stage j and treatment k

MAC-snSMART Borrowing Structure



MAC-snSMART Method

► Control Arm:

External Control	New Trial
$Y_i \theta_i \sim N(\theta_i, s_i^2)$ with prob $p_i, \theta_i \mu_p \sim N(\mu_p, \tau_i^2)$ with prob $1 - p_i, \theta_i \sim N(m_i, v_i^2)$	$Y_{1p} \theta_{1p} \sim N(\theta_{1p}, s_{1p}^2)$ with prob $p_{1p}, \theta_{1p} \mu_p \sim N(\mu_p, \tau_{1p}^2)$ with prob $1 - p_{1p}, \theta_{1p} \sim N(m_{1p}, v_{1p}^2)$

► Treatment Arms:

$$\begin{bmatrix} Y_{1k} \\ Y_{2k'} \end{bmatrix} \sim MVN \left(\begin{bmatrix} \theta_{1k} + b \\ \theta_{2k'} \end{bmatrix}, \begin{bmatrix} s_{1k}^2 & s_{kk'} s_{1k} s_{2k'} \\ s_{kk'} s_{1k} s_{2k'} & s_{2k'}^2 \end{bmatrix} \right)$$

where $k = p, l, h; k' = l, h$. Note, b is a selection bias correction term. s_{jk} can be estimated based on observed data in the current snSMART. $s_{kk'}$ denotes the correlation between stage 1 trt k outcomes and stage 2 trt k' outcomes.

$$\theta_{1k}, \theta_{2k} \sim N(\mu_k, \tau_k^2); k = l, h$$

Bayesian Priors

We suggest half-normal priors for all non-negative parameters, $Unif(-1,1)$ for $s_{kk'}$, the correlation parameter, and weakly informative normal priors for all other parameters.

Specifically,

1. Weakly informative normal priors: μ_p, μ_k , and b
2. Half-normal priors: $\tau_i, \tau_{1p}, \tau_k$

The values of prior means and prior standard deviations are elicited from expert opinion and historic knowledge.

Simulation Settings

1. Generate simulated data sets
2. Analyze data using traditional method / MAC-snSMART / robust MAC-snSMART
3. Compare bias, rMSE, coverage and width of the 95% credible interval

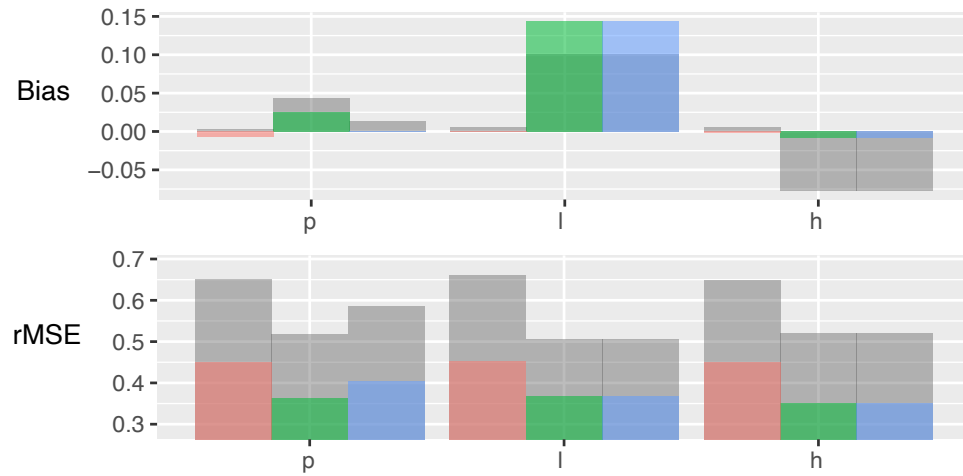
	Parameters	Scenarios				
		1	2	3	4	5
Data Generating Process 1	θ_i	0	0	0	0	0 or 1*
	θ_{1p}	0	0	0	0	0
	θ_{1l}	0	0	2	4	4
	θ_{1h}	0	6	6	8	8
Data Generating Process 2	θ_i	0	0	0	0	0 or 1*
	θ_{1p}	0	0	0	0	0
	θ_{1l}, θ_{2l}	0, 1	0, 1	2, 3	4, 5	4, 5
	θ_{1h}, θ_{2h}	0, 1	0, 1	6, 7	8, 9	8, 9

* The external controls and current trial data are not entirely aligned

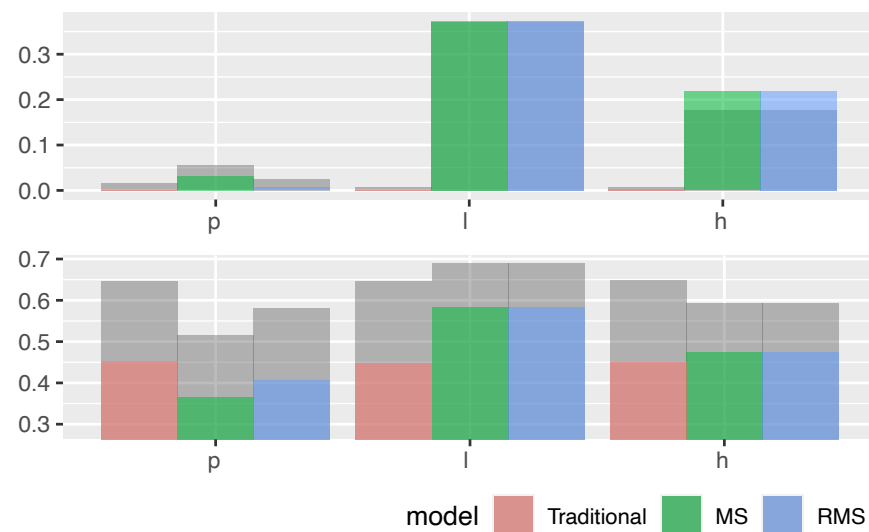
Simulation Results

Simulation results of Scenario 5:

External control non-exchangeable,
Stage-wise exchangeable



External control non-exchangeable,
Stage-wise non-exchangeable



Example Data Analysis

► External Controls:

Data from participants from the **CINRG DNHS** who met the **eligibility criteria** of the SPITFIRE trial and had NSAA total score or 6MWD records.

► Current Trial:

Based on the SPITFIRE trial protocol, we simulated stage 1 patient-level data, categorized participants as stage 1 responders and nonresponders, and randomly generated Stage 2 outcomes.

We analyzed the data with the robust **MAC-snSMART** method, the **BJSM** (Bayesian Joint Stage model), and the **traditional** method.

Example Data Analysis

► NSAA Results:

Estimator	Original Result	BJSM	RMS
$\hat{\theta}_{1p}$	-2.99 (-4.26, -1.71)	-2.91 (-4.01, -1.82)	-2.89 (-3.68, -2.10)
$\hat{\theta}_{1l}$	-3.44 (-4.75, -2.13)	-3.38 (-4.34, -2.41)	-3.40 (-4.49, -2.31)
$\hat{\theta}_{1h}$	-2.41 (-3.66, -1.16)	-2.42 (-3.35, -1.48)	-2.49 (-3.56, -1.42)
$\hat{\theta}_{1l} - \hat{\theta}_{1p}$	-0.45 (-2.17, 1.27)	-0.46 (-1.91, 0.98)	-0.52 (-1.88, 0.83)
$\hat{\theta}_{1h} - \hat{\theta}_{1p}$	0.58 (-1.10, 2.26)	0.50 (-0.93, 1.92)	0.40 (-0.94, 1.74)

Example Data Analysis

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$\hat{\theta}_{1h} - \hat{\theta}_{1p}$	0.58 (-1.10, 2.26)	0.50 (-0.93, 1.92)	0.40 (-0.94, 1.74)

Estimators obtained from the robust **MAC-snSMART** method and **BJSM** are consistent with each other and have **significantly smaller 95% CI width** than the traditional method because of the efficient use of data across **both** stages.

Conclusions

- ▶ Robust MAC-snSMART method estimates treatment effects of placebo, low and high doses in an snSMART design with a continuous outcome and formally incorporates **external control data**.
- ▶ snSMART design and robust MAC-snSMART method are appropriate for diseases that stay relatively **stable** over the trial period.
- ▶ Robust MAC-snSMART method assumes exchangeable treatment effects across trial stages, can be extended to include treatment effect non-exchangeability.
- ▶ MAC-snSMART method provides **power gains** compared to traditional methods, lead to a higher level of evidence in rare disease dose-finding trials.

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Appendix

About the SPITFIRE trial:

This is a multi-center, randomized, double-blind, placebo-controlled study to assess the efficacy, safety and tolerability of two different weekly doses of RO7239361 in ambulatory boys with Duchenne Muscular Dystrophy (DMD).

► Inclusion Criteria:

Diagnosed with DMD by confirmed medical history and genetic testing

Able to walk without assistance

Minimum North Star Ambulatory Assessment score of 15 at screening

Able to walk up 4 stairs in 8 seconds or less

Weigh at least 15 kg (33 lbs)

Taking corticosteroids for DMD

Appendix

b is a selection bias correction term. The selection bias is due to the design since those who receive low dose and those who receive high dose and do not respond are not re-randomized. Given that we know which treatment sequences the participants follow, to account for the difference in stage 1 mean, the bias correction term is defined as:

$$b = I(k = l, k' = l)b_{ll} - I(k = l, k' = h)b_{lh} - I(k = h)b_h$$

Explicitly, b_{ll} denotes the expected difference between the stage 1 mean treatment effect of group $(1l, 2l)$ and the overall stage 1 low dose mean treatment effect, b_{lh} denotes the expected difference between the stage 1 mean treatment effect of group $(1l, 2h)$ and the overall stage 1 low dose mean treatment effect, and similarly, b_h denotes the expected difference between the stage 1 mean treatment effect of high dose responders and the overall stage 1 high dose mean treatment effect.

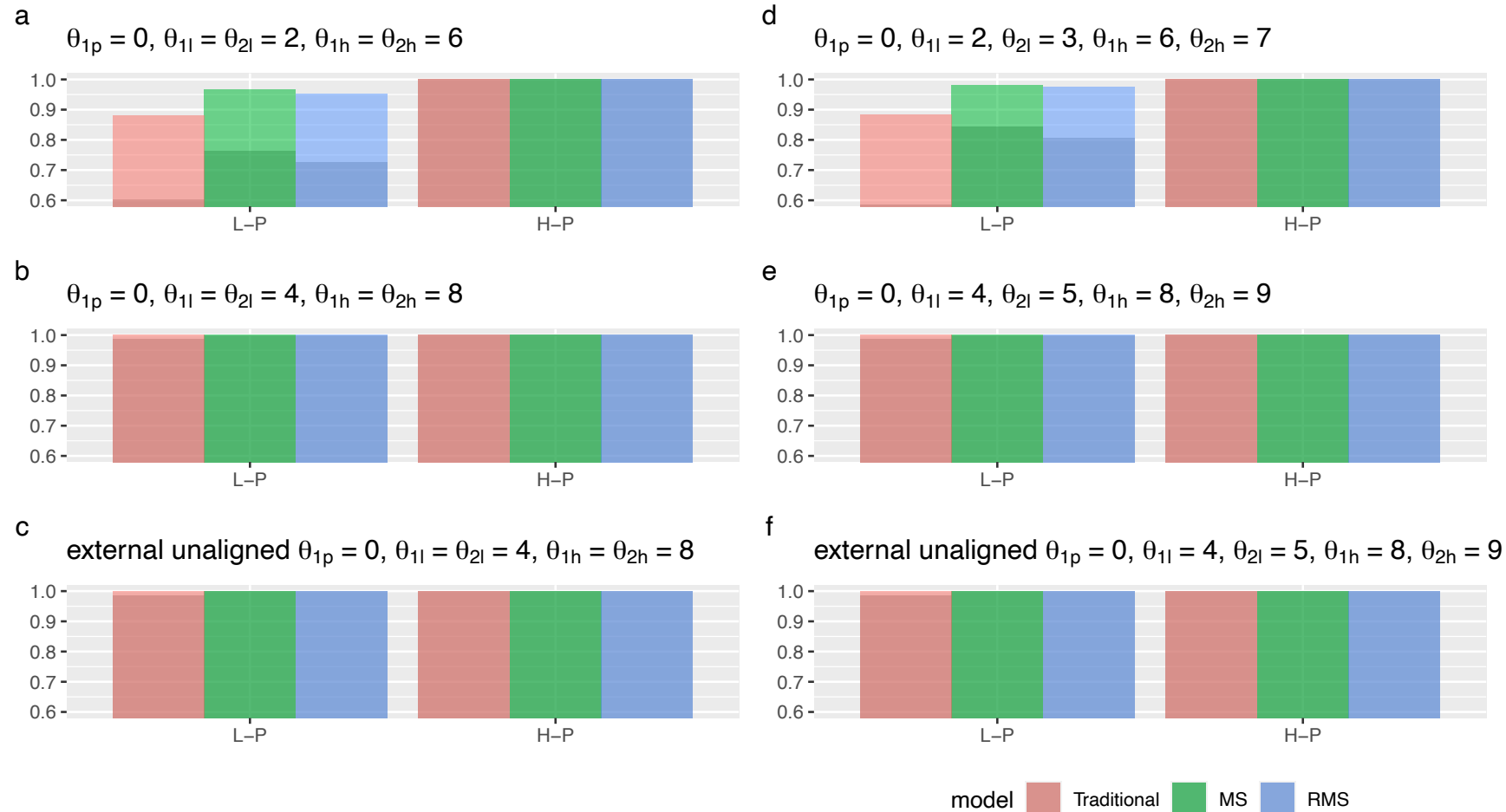
Appendix

B_{ll} , B_{lh} and B_h , the observed differences corresponding to b_{ll} , b_{lh} and b_h , follow normal distributions $N(b_{ll}, \xi_{ll}^2)$, $N(b_{lh}, \xi_{lh}^2)$ and $N(b_h, \xi_h^2)$, respectively.

Appendix

Simulated power of all methods:

Power



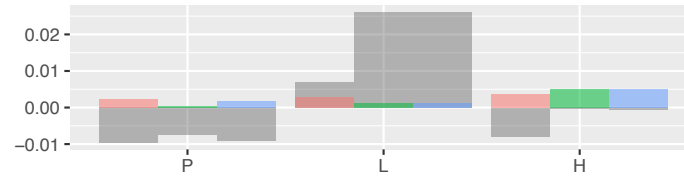
Appendix

Simulation Outcome: Bias

Bias

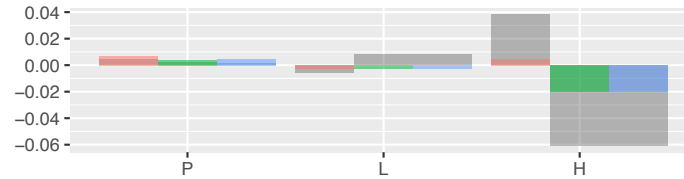
a

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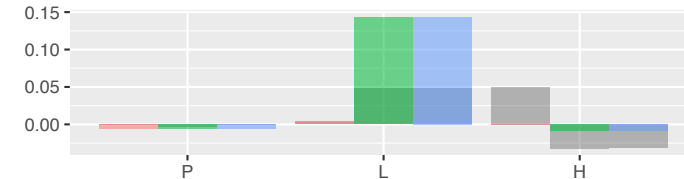
b

$$\theta_{1p} = 0, \theta_{1l} = \theta_{2l} = 0, \theta_{1h} = \theta_{2h} = 6$$



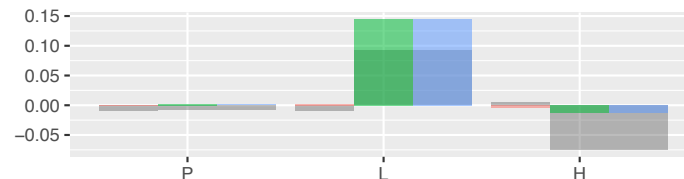
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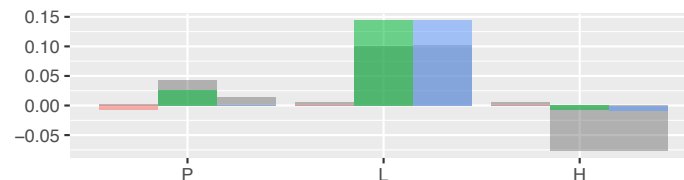
d

$$\theta_{1p} = 0, \theta_{1l} = \theta_{2l} = 4, \theta_{1h} = \theta_{2h} = 8$$



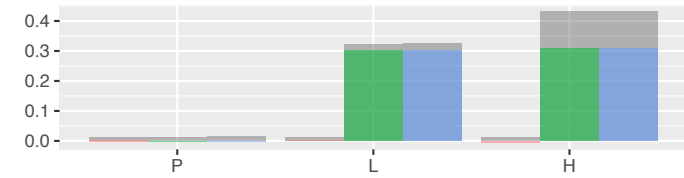
e

external unaligned $\theta_{1p} = 0, \theta_{1l} = \theta_{2l} = 4, \theta_{1h} = \theta_{2h} = 8$



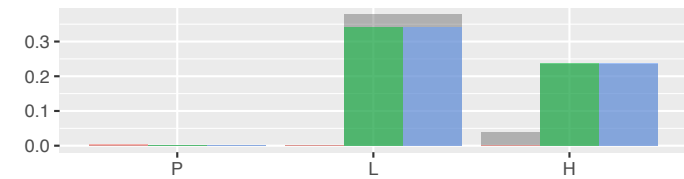
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$$\theta_{1p} = 0, \theta_{1l} = 0, \theta_{2l} = 1, \theta_{1h} = 0, \theta_{2h} = 1$$



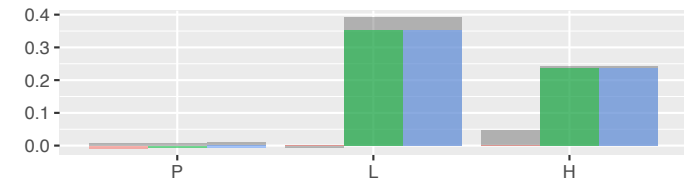
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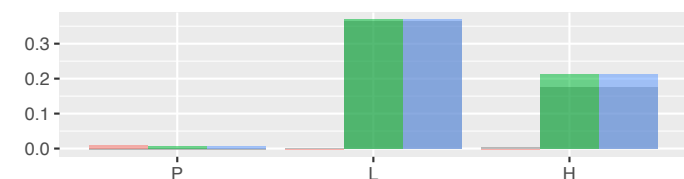
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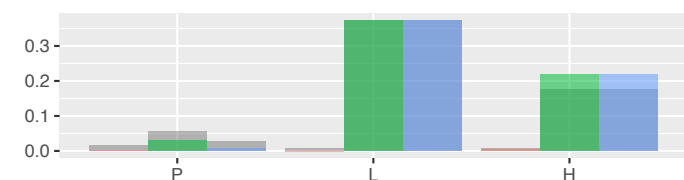
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j

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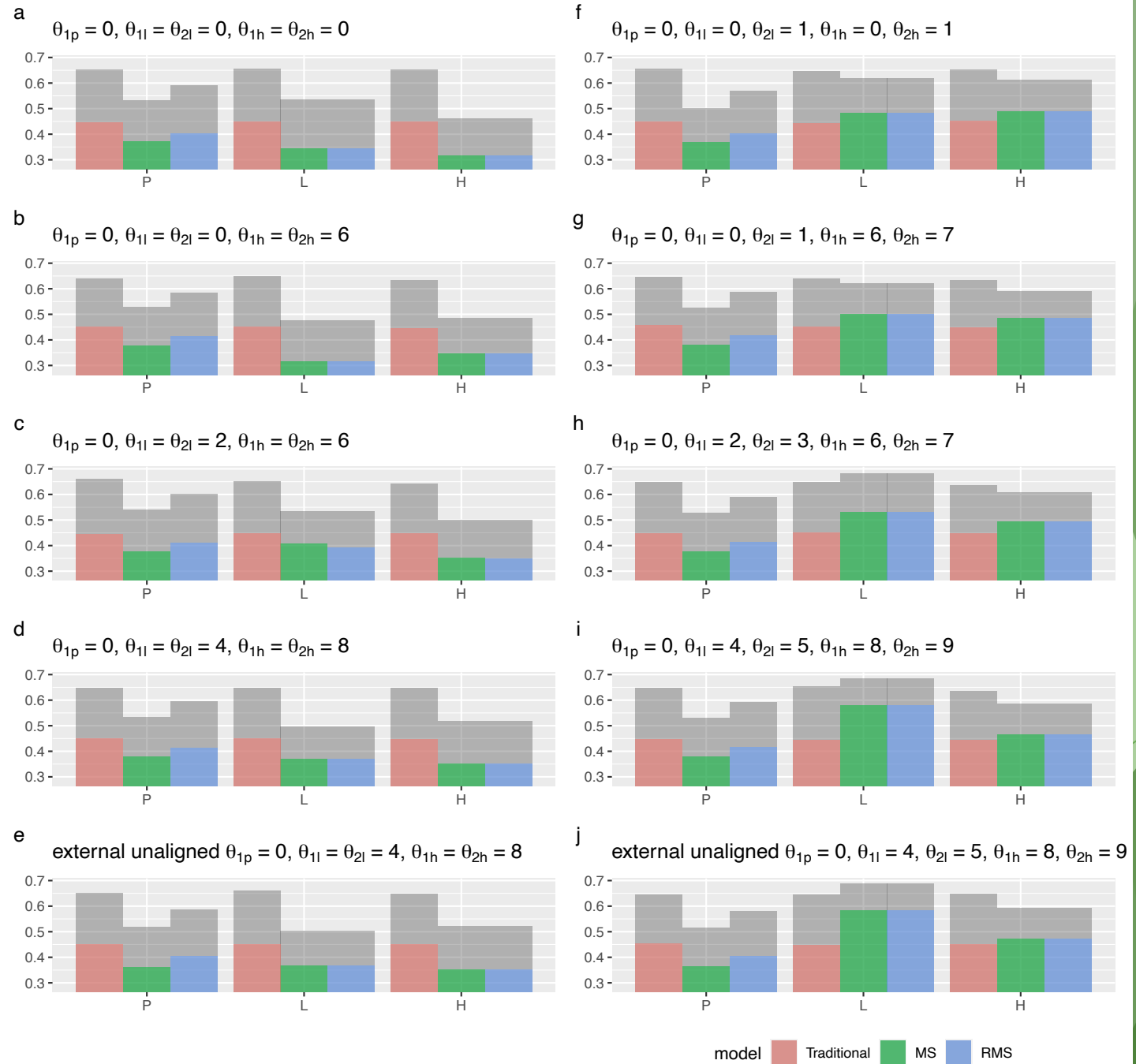


model Traditional MS RMS

Appendix

Simulation Outcome: rMSE

rMSE

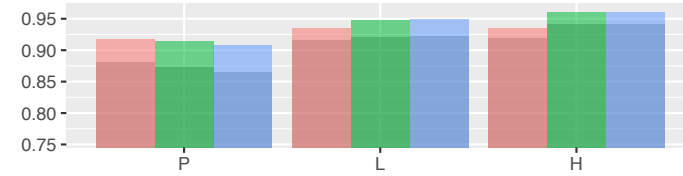


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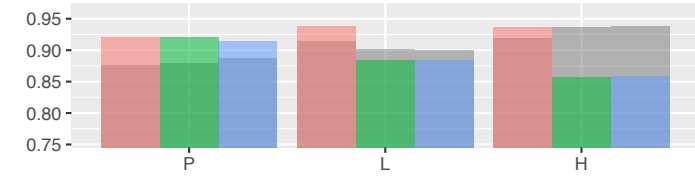
Simulation Outcome: CR

CR

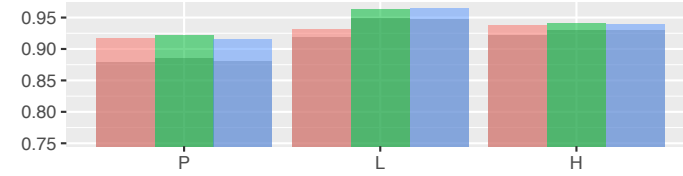
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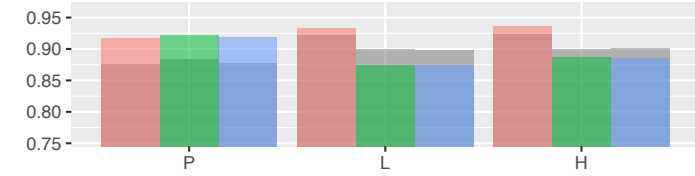
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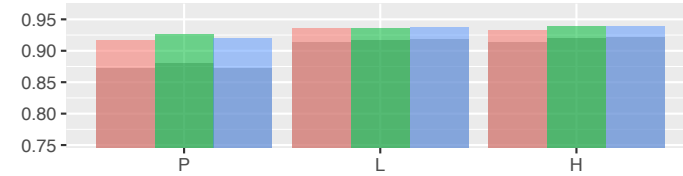
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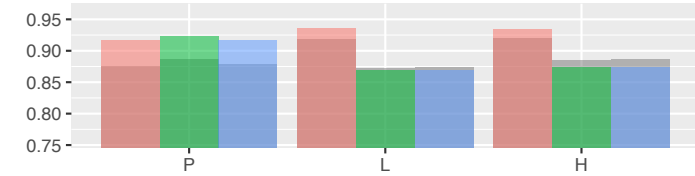
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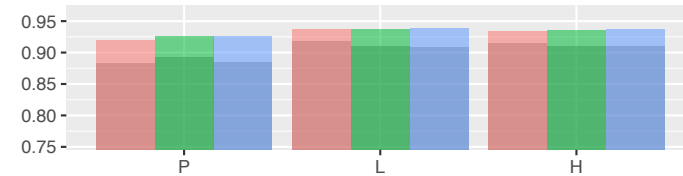
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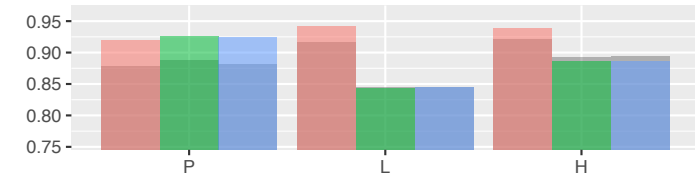
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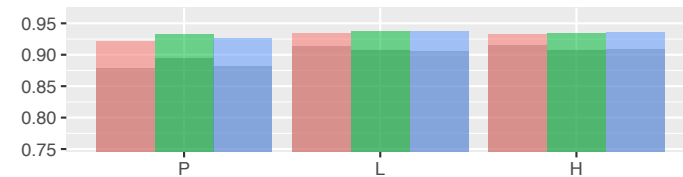
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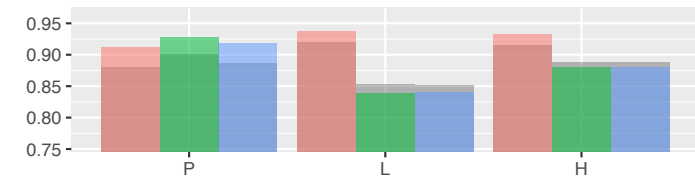
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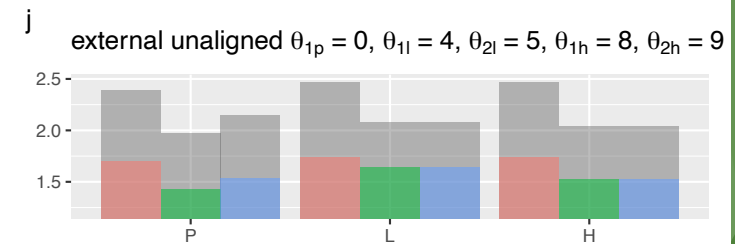
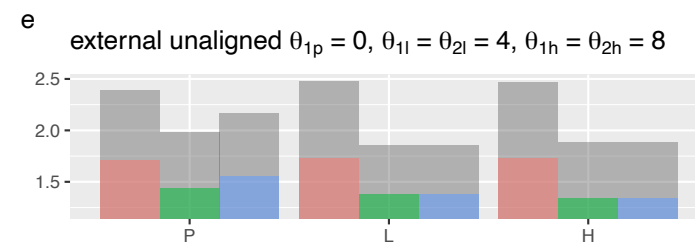
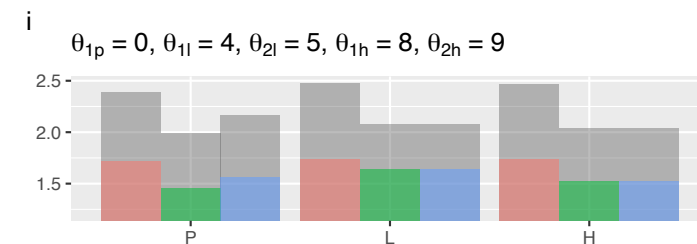
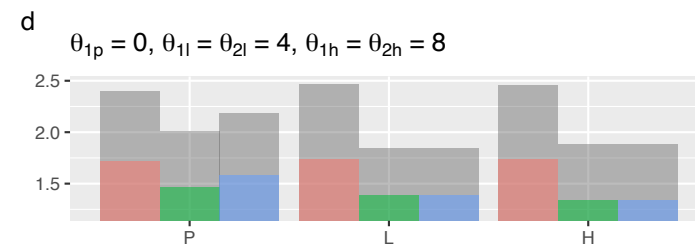
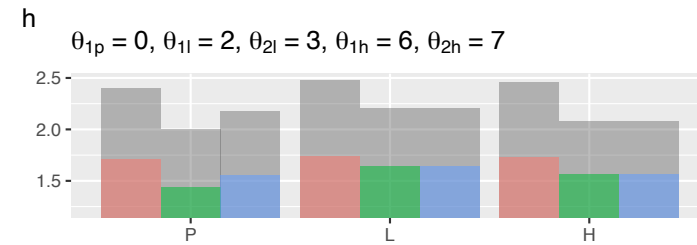
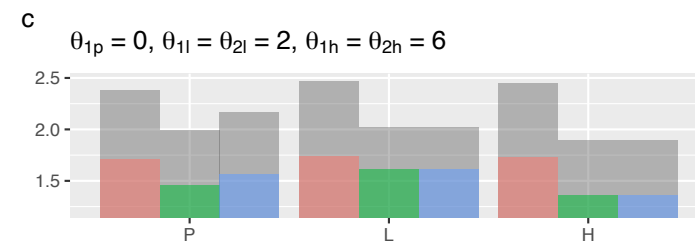
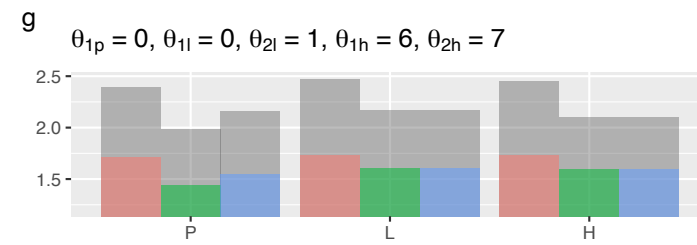
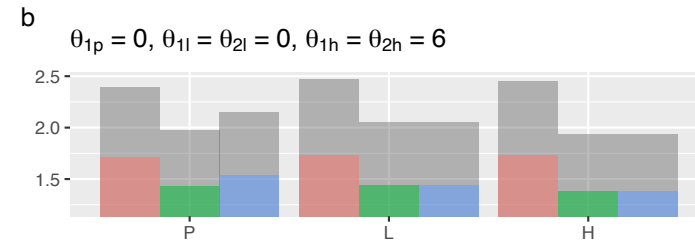
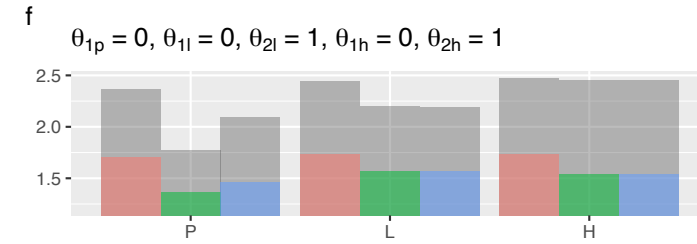
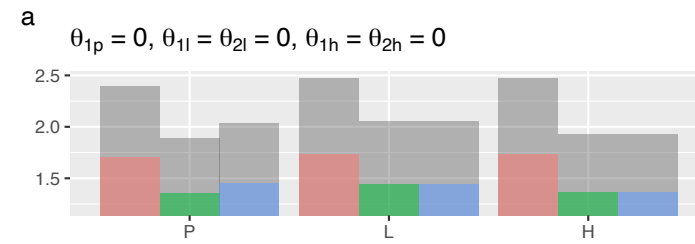


model Traditional MS RMS

Appendix

Simulation Outcome: Width

Width



model Traditional MS RMS

Appendix

Simulated type I error:

Sample Size	Traditional		MS		RMS	
	Low	High	Low	High	Low	High
Data generating process 1						
$N = 50$	0.070	0.059	0.039	0.018	0.042	0.022
$N = 25$	0.077	0.076	0.056	0.026	0.059	0.030
Data generating process 2						
$N = 50$	0.057	0.059	0.061	0.056	0.065	0.060
$N = 25$	0.076	0.080	0.070	0.053	0.075	0.058

Appendix - Example Data Analysis

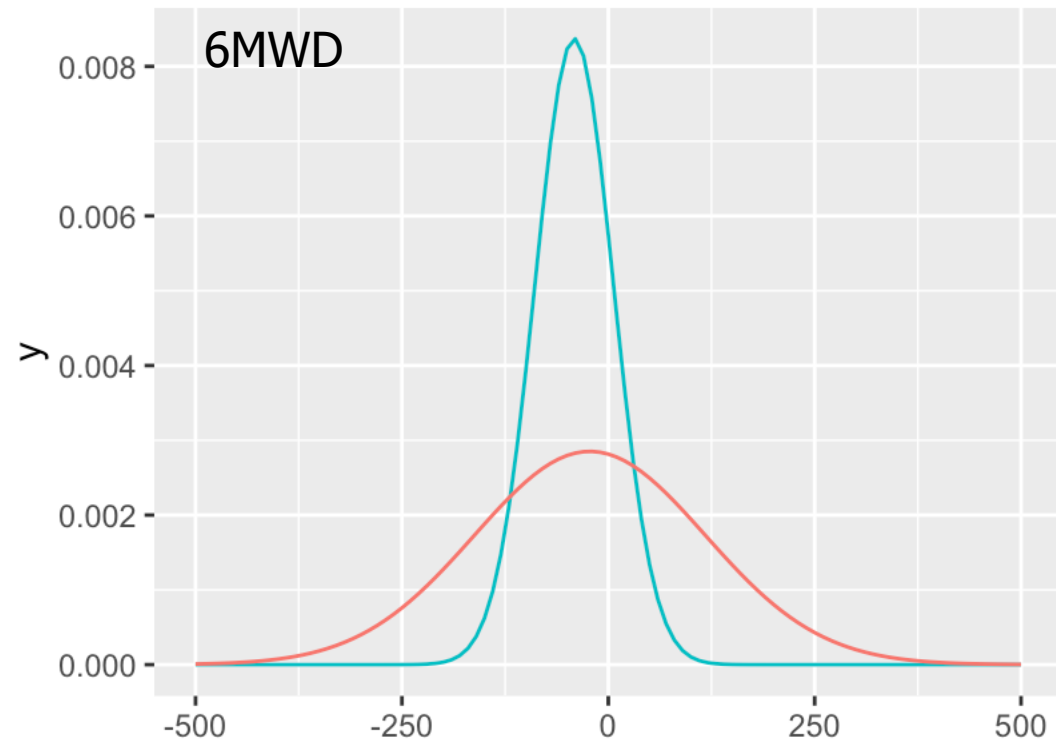
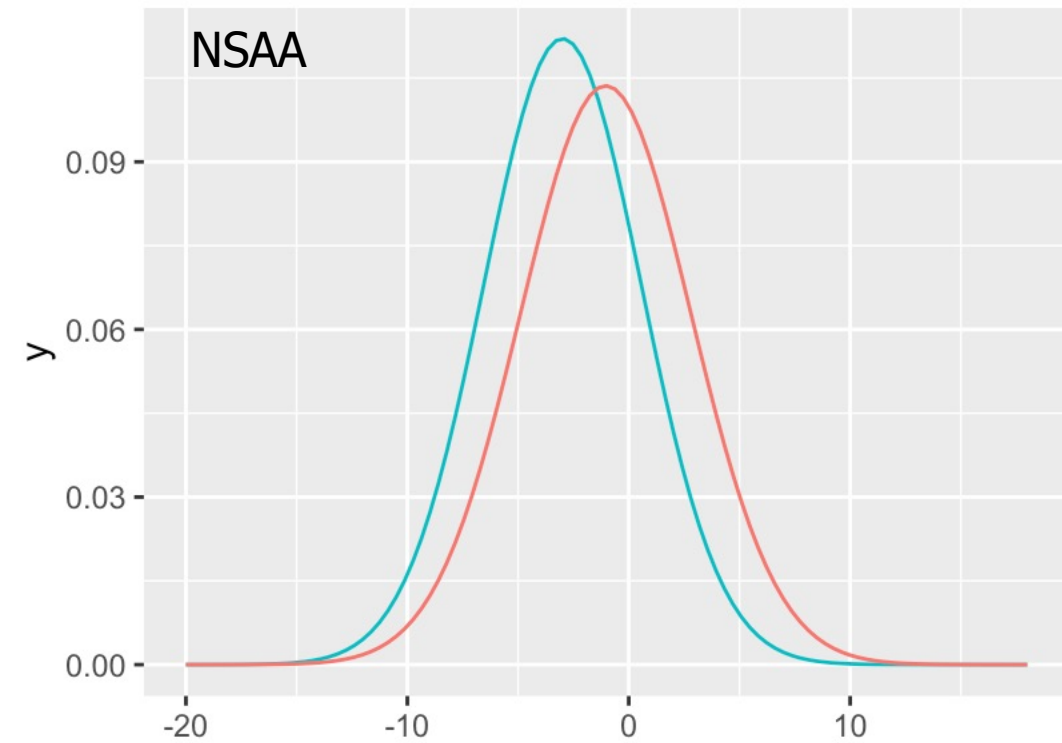
► 6-Minute Walk Distance (6MWD) Results:

Estimator	Original Result	BJSM	RMS
$\hat{\theta}_{1p}$	-41.3 (-58.4, -24.2)	-41.1 (-54.4, -27.8)	-41.0 (-52.5, -29.3)
$\hat{\theta}_{1l}$	-39.6 (-57.2, -22.0)	-39.3 (-51.6, -27.6)	-39.4 (-53.2, -26.1)
$\hat{\theta}_{1h}$	-30.0 (-47.1, -12.9)	-29.7 (-40.8, -18.7)	-30.2 (-42.1, -18.0)
$\hat{\theta}_{1l} - \hat{\theta}_{1p}$	1.7 (-21.1, 24.6)	1.8 (-16.6, 19.5)	1.6 (-15.6, 19.1)
$\hat{\theta}_{1h} - \hat{\theta}_{1p}$	11.3 (-11.0, 33.6)	11.4 (-5.8, 28.6)	10.9 (-6.4, 28.1)

Appendix

► Example data analysis

SPITFIRE placebo arm vs CINRG external control



colour

- External Control
- Placebo Arm