Small Sample Sequential Multiple Assignment Randomized Trials with Continuous Repeated Measures

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Holly Hartman

Roy Tamura, Matthew Schipper, Kelley Kidwell

holhart@umich.edu
https://holly-hartman.com
@holly7holly

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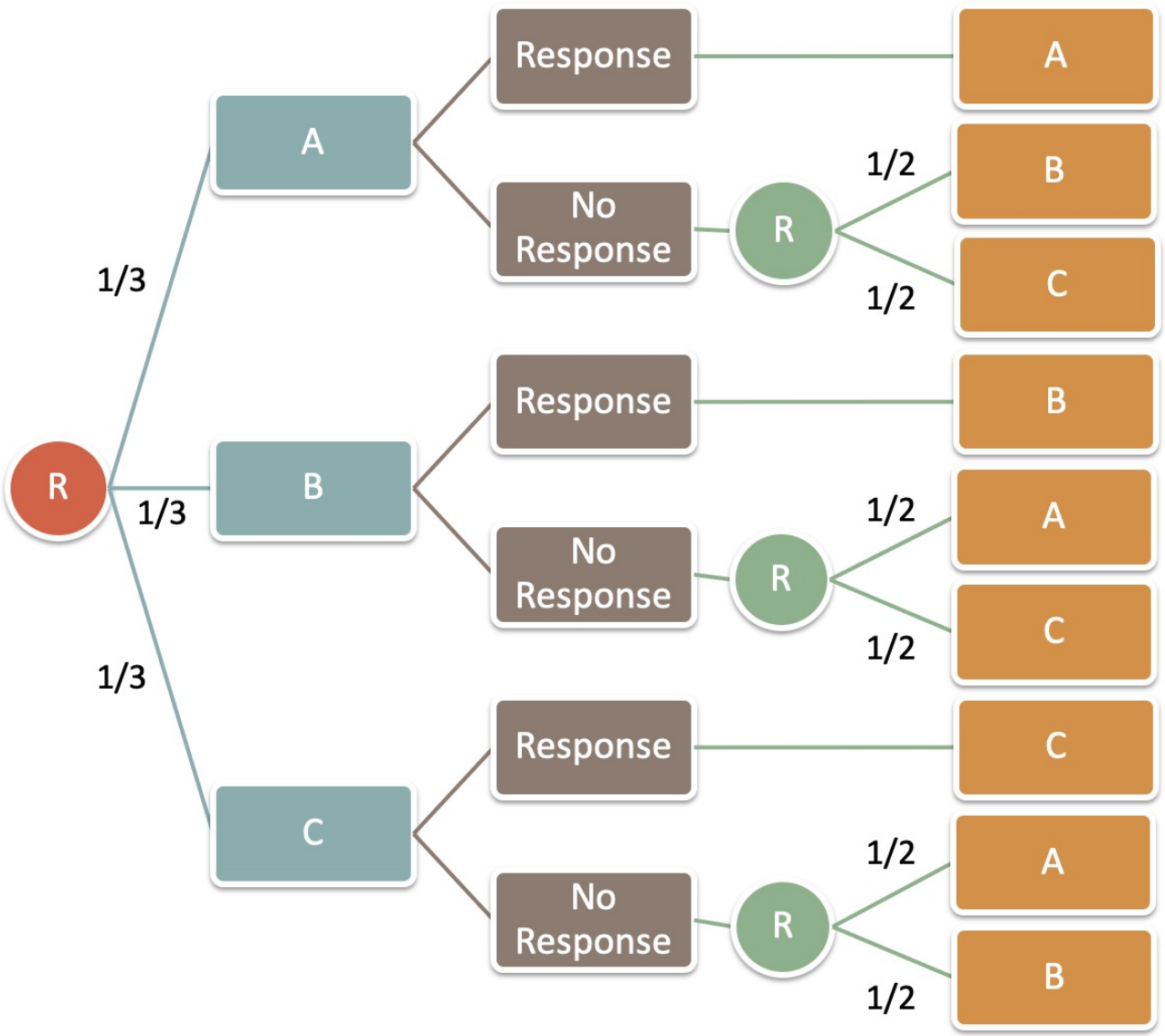
snSMART Goals

- snSMARTs designs can be used to more efficiently identify the best treatment overall and use Bayesian methods [1, 2].
- Both require dichotomous determination of "response" to determine the second stage treatment (sometimes called a tailoring variable) [3, 4].

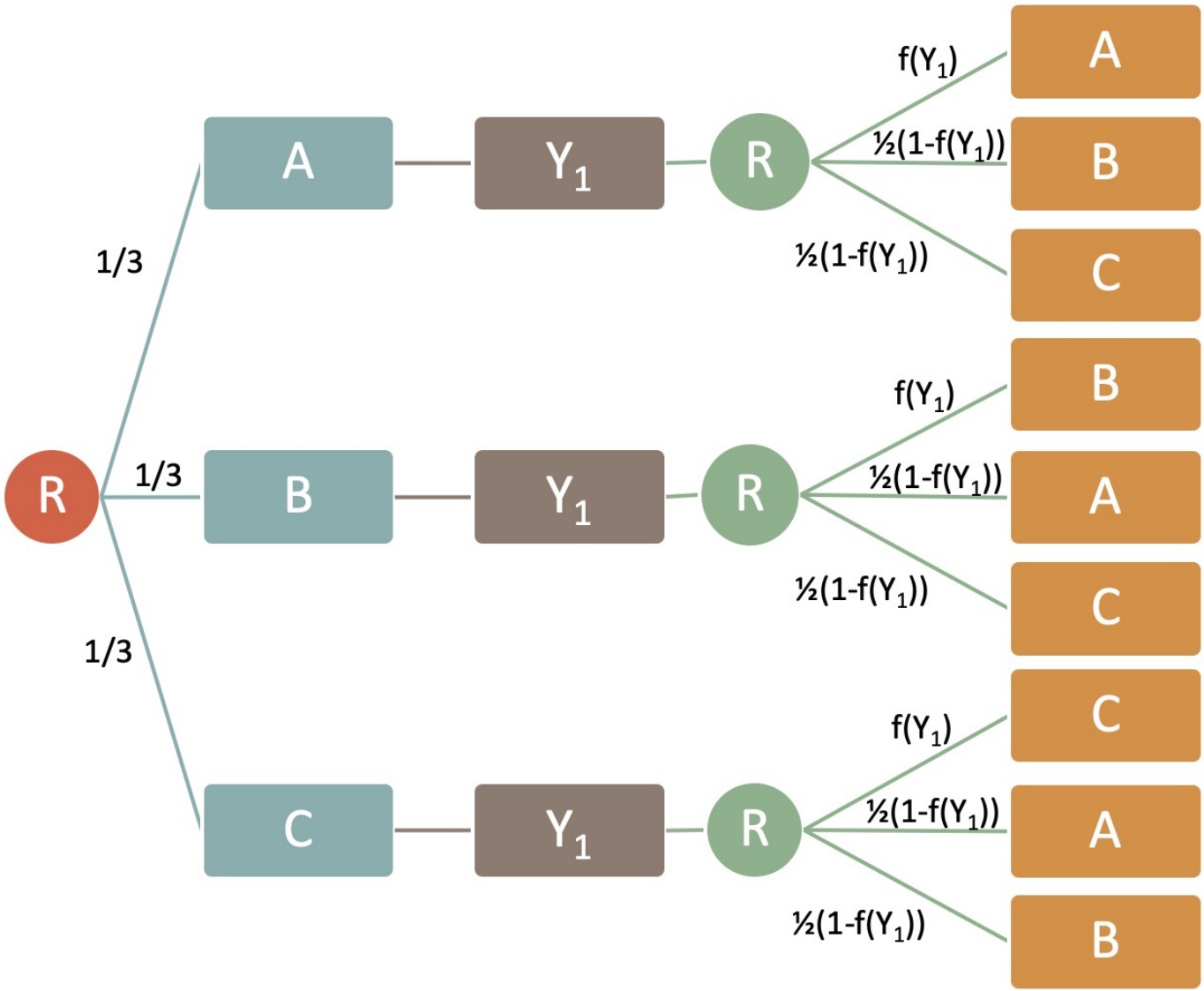
snSMART Design



Problems with binary outcomes

- In rare diseases or other areas with little prior knowledge, a clear choice for a dichotomization method or a binary surrogate may not be available prior to the start of the study.
- Pilot studies can be expensive and cost prohibitive.
- If a dichotomized continuous variable is used as outcome, can result in loss of statistical power [5].

Continuous snSMART Design



snSMART design with continuous repeated measures

- Goal: identify the best treatment at the end of the first stage.
- Use a mapping function to map first stage outcome Y_{i1} to $[0, 1]$ and is the probability of staying on the same treatment.
- Better outcomes of Y_{i1} should map to values closer to 1
- Options for the Mapping Function:
  - Linear function between minimum and maximum values of Y_1
    - $f(Y_1) = (Y_1 - Y_{min})/(Y_{max} - Y_{min})$
    - Can also modify with powers, $f(Y_1)^k$, if distribution is expected to be skewed or it would be beneficial to have more/fewer people stay on the treatment
  - Function between practical/ethical values of Y_1 and 0 or 1 beyond these limits

Models

Goal (mathematically): Estimate all β_j parameters (treatment effects at the end of the first stage).
Mean Model:

$$\mu_1(T_{i1}) = \sum_{j=1}^{T} \beta_j I(T_{i1} = j)$$

$$\mu_2(T_{i1}, T_{i2}) = \alpha_1 \sum_{j=1}^{T} \beta_j I(T_{i1} = j) + \alpha_2 \sum_{k=1}^{T} \beta_k I(T_{i2} = k) + \alpha_3 I(T_{i1} = T_{i2})$$

Covariance Model:

$$\mathbf{V}(T_{i1}, T_{i,2}) = V_1 I(T_{i1} = T_{i2}) + V_2 I(T_{i1} \neq T_{i2})$$

where V_1 and V_2 are both 2×2 variance-covariance matrices.

Priors

$$\beta_j \sim N(\text{mean} = 50, \text{standard deviation (sd)} = 50) \text{ for all } j$$
$$\alpha_1 \sim Unif(0, 0.5)$$
$$\alpha_3 \sim FN(\text{mean} = 0, \text{sd} = 20)$$
$$V_1 \sim W_2\left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, 2\right)$$
$$V_2 \sim W_2\left(\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, 2\right)$$

These priors impose 3 conditions for the α parameters:

1) $\alpha_2 = 1 - \alpha_1$
2) $\alpha_2 > \alpha_1$
3) $\alpha_3 \geq 0$

Ideal scenarios

- $\alpha = (0.2, 0.8, 5)$

$$V_1 = \sigma^2 \begin{bmatrix} 1 & \tau_1 \\ \tau_1 & 1 \end{bmatrix}, V_2 = \sigma^2 \begin{bmatrix} 1 & \tau_2 \\ \tau_2 & 1 \end{bmatrix}$$

- $\tau_1 = 0.8$, $\tau_2 = 0.3$, and $\sigma = 20$

	β		
Scenario	1	2	3
1	40	50	60
2	20	30	40
3	60	70	80

Scenarios with model assumption violations

- We examined 3 assumption violations
  - Second stage treatment effect, μ_2, is based on the treatment specific pathway (TSP) rather than weighted means
  - Variance, σ^2, varies depending on treatment
  - Correlation, τ, depends on the TSP (treatments may have more or less correlation based on treatment mechanism similarities)
- All other parameters were the same as scenario 1.

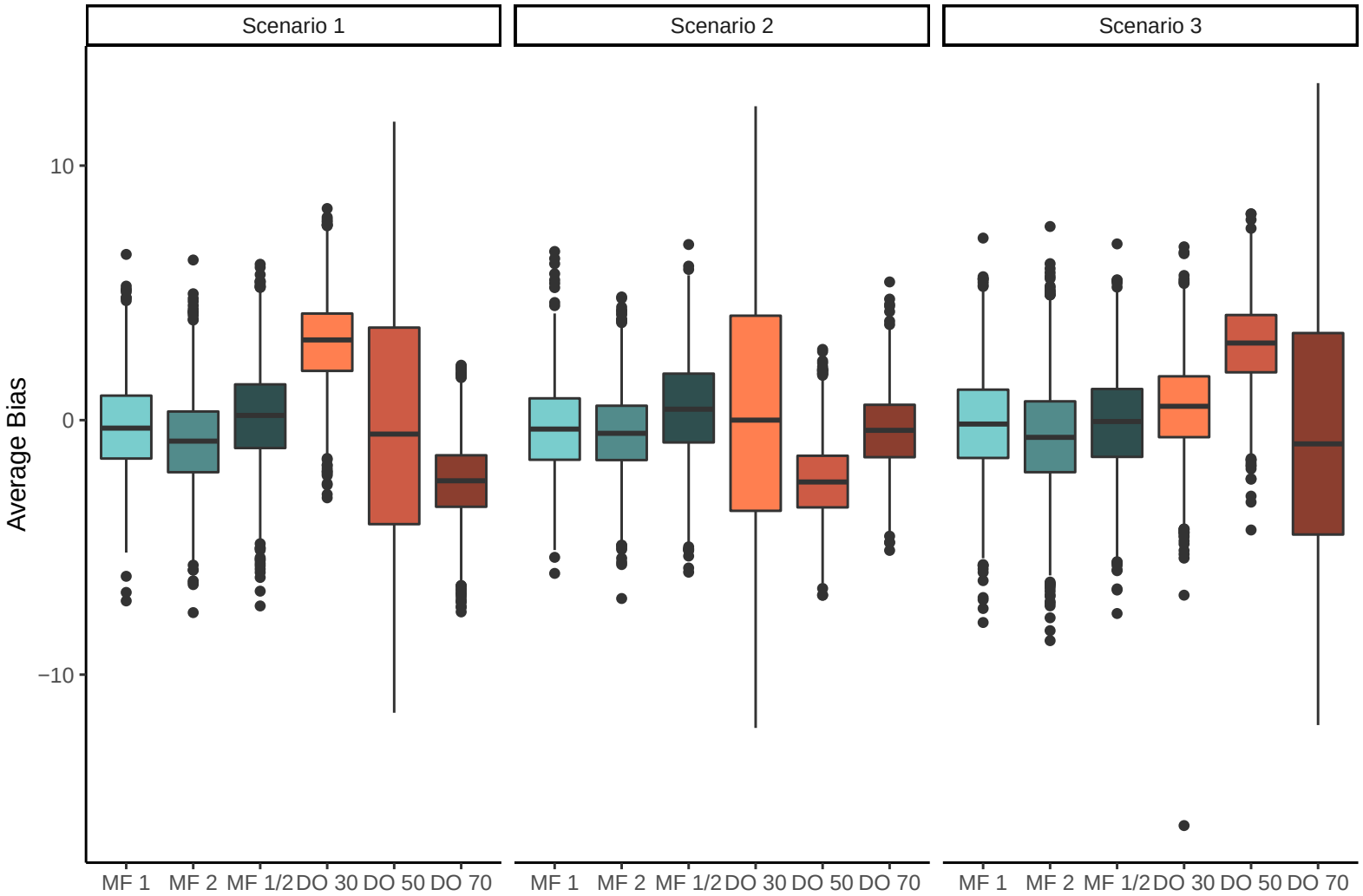
Scenarios

	β			Violation		
Scenario	1	2	3	Mean	Variance	Correlation
1	40	50	60			
2	20	30	40			
3	60	70	80			
4	40	50	60	×		
5	40	50	60		×	
6	40	50	60			×
7	40	50	60	×	×	
8	40	50	60	×		×
9	40	50	60		×	×
10	40	50	60	×	×	×

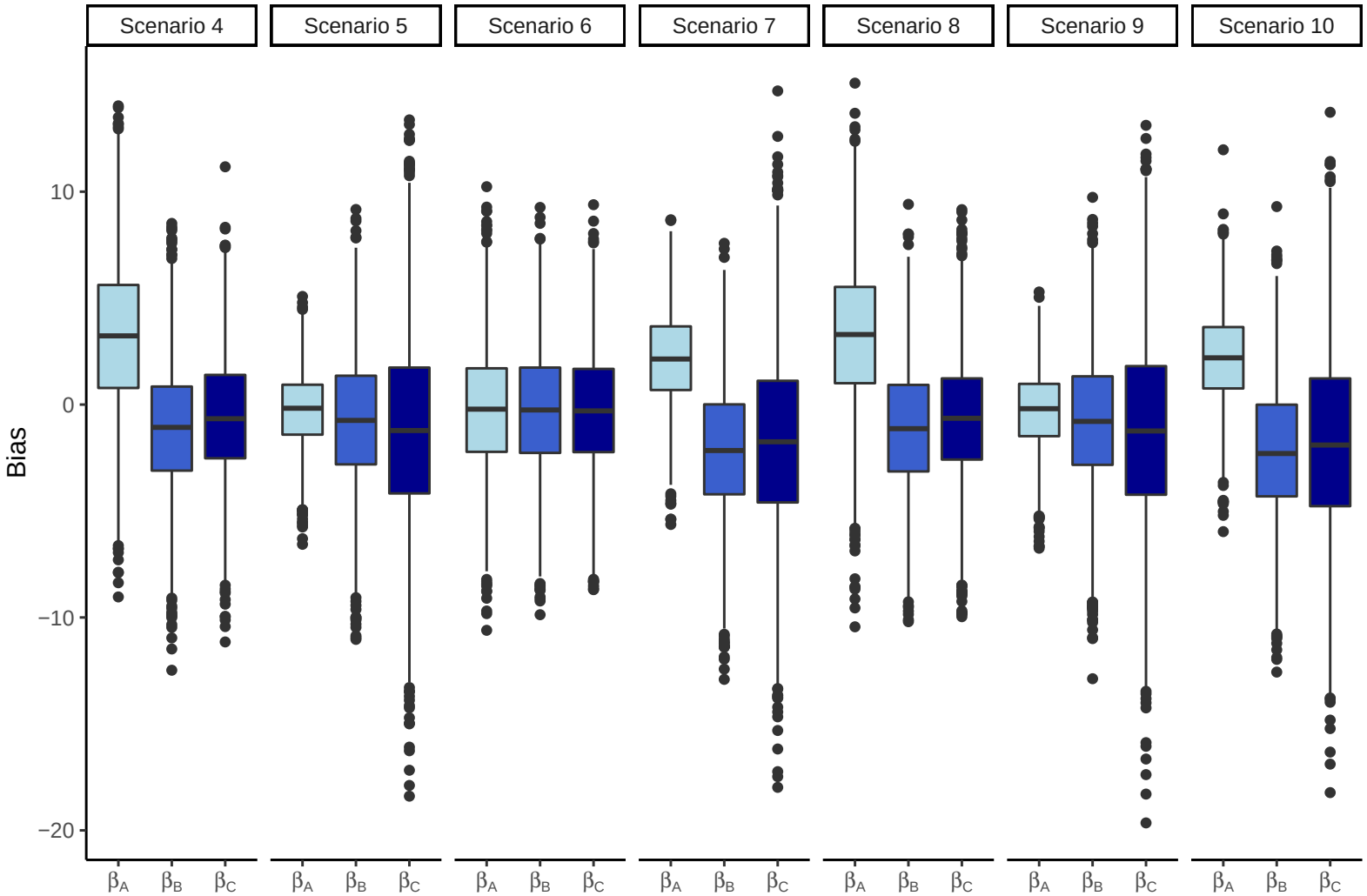
Mapping functions

- Used 3 mapping functions
  - $MF1 = Y_1/100$
  - $MF2 = (Y_1/100)^2$
  - $MF1/2 = (Y_1/100)^{1/2}$
- For scenarios 1, 2, and 3 compared to dichotomized outcomes (DO) using dichotomization of the continuous first stage outcome with 3 different cut offs:
  - DO 30 = 30
  - DO 50 = 50
  - DO 70 = 70

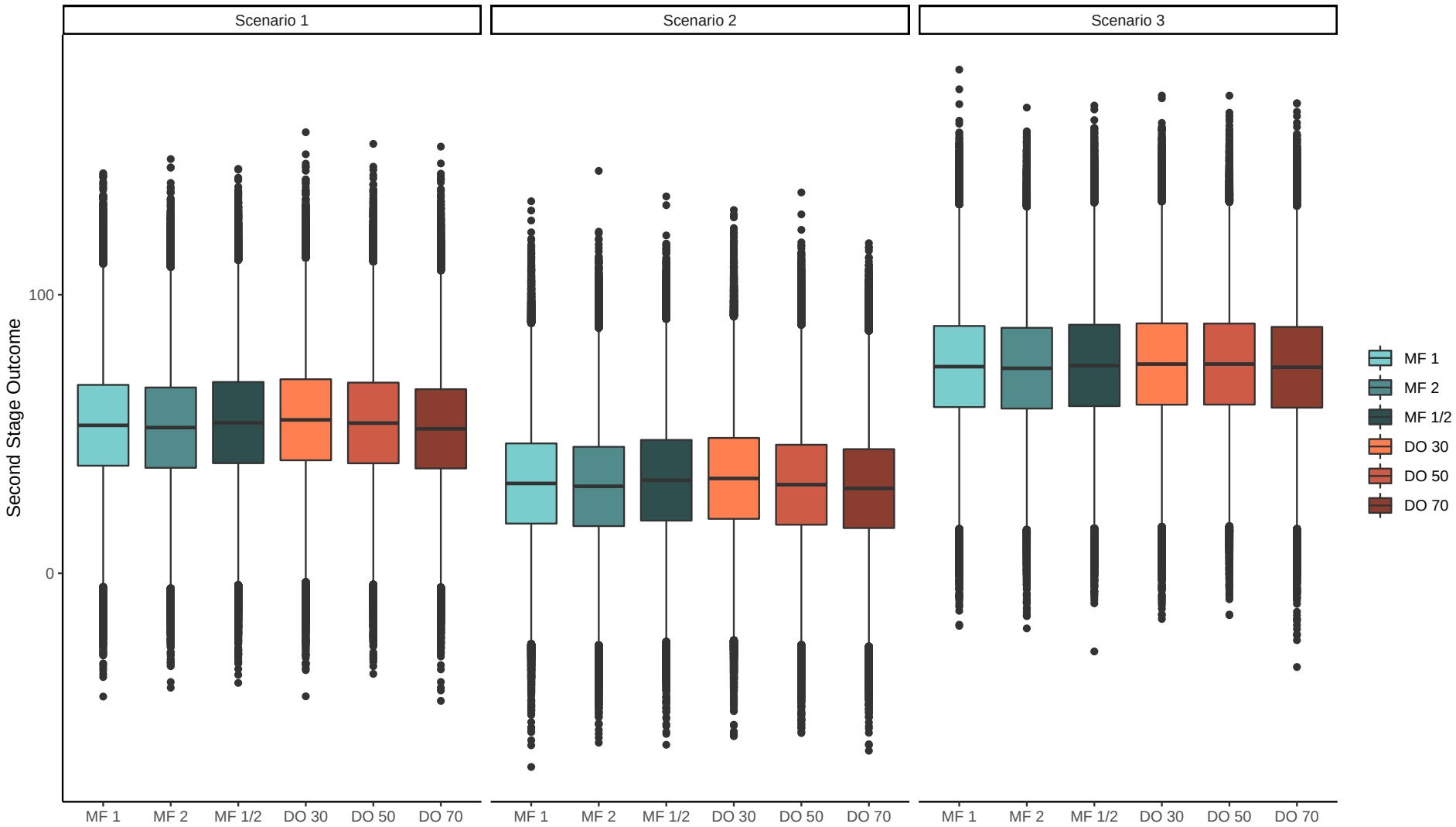
Results for ideal scenarios



Results for model assumption violations



Patient outcomes



Conclusions

- Mapping functions are a reasonable method for conducting a snSMART design in the absence of a binary variable.
- Patient outcomes are similar to when using a dichotomous outcome.
- Using a mapping function improves the number of treatment pathways seen in a trial relative to a poorly selected dichotomous outcome.

References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