Blinded Sample Size Re-estimation for Adaptive Enrichment Designs with Longitudinal Data

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Workshop: Adaptive Designs and Multiple Testing Procedures

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„BIOSTATISTISCHE METHODEN ZUR EFFIZIENTEN EVALUATION VON INDIVIDUALISIERTEN THERAPIEN (BIMIT)“

Outline

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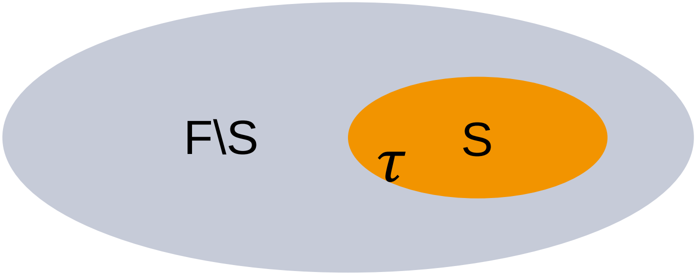
Motivation



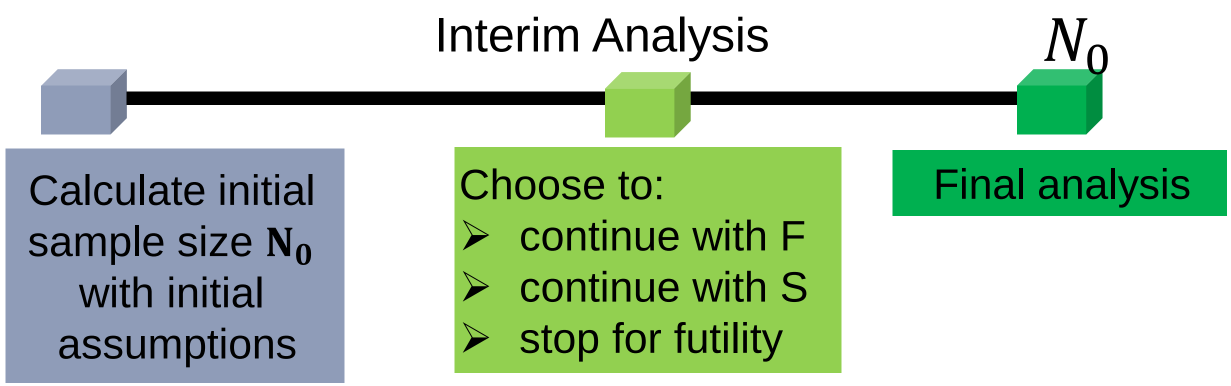
- One major goal in personalized/stratified medicine is the identification of subgroups (S)
- These subgroups might yield higher efficacy or provide a better safety profile
- A requirement for adaptive enrichment designs are identifiable subgroups within the population of interest (F) by e.g. genetic markers

Adaptive Enrichment Design (AED)

- **Step 1**: calculate sample size based on initial assumptions about nuisance parameters and recruit subjects from full-population
- **Interim Analysis**: based on a decision rule choose to…
  - …continue study with…
    - … full-population
    - … sub-population (enrichment)
  - …stop study for futility

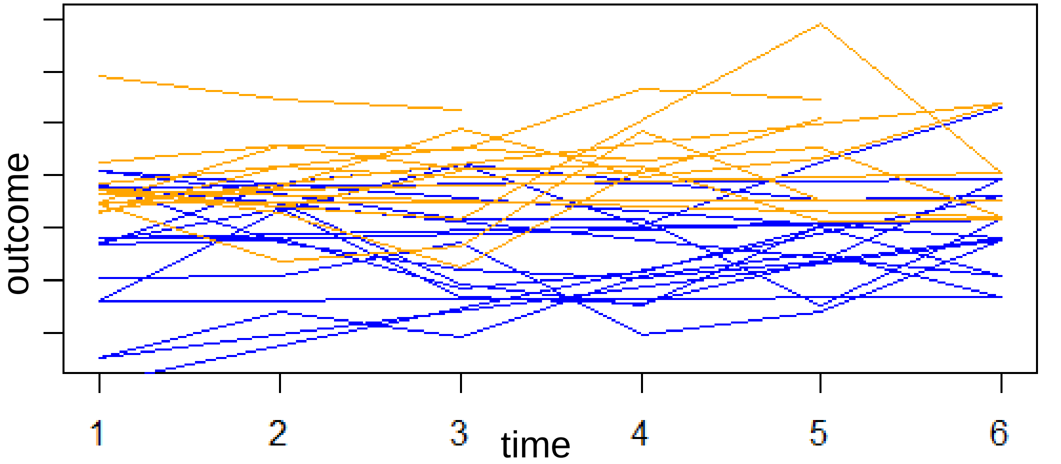
  …based on collected data and a pre-defined selection rule

- **Final analysis**: test for efficacy using combination tests



Datatype

- Repeated measurements



- In this setting: missingness based on MCAR dropouts

Pat ID	Time					
	t_0	t_1	t_2	t_3	t_4	t_5
1	2.4	2.8	-	-	-	-
2	2.6	2.8	3.0	3.3	3.5	3.6
3	2.8	3.1	3.1	3.2	-	-
4	2.5	2.8	2.9	3.1	3.3	3.4

Statistical Model

- Estimation of linear trends for repeated measures

$$y_{ijk}^{\{G\}} = \beta_1^{\{G\}} + \beta_2^{\{G\}} \cdot j + \beta_3^{\{G\}} \cdot 1_{\{k=\text{Treat}\}} + \beta_4^{\{G\}} \cdot j \cdot 1_{\{k=\text{Treat}\}} + \epsilon_{ijk}^{\{G\}}$$

$$\text{cor}\left(y_{ijk}, y_{ihk}\right) = \rho^{|j-h|}; \text{cor}\left(y_{ijk}, y_{oj'k'}\right) = 0;\ \epsilon_{ijk} \sim N(0, \sigma^2)$$

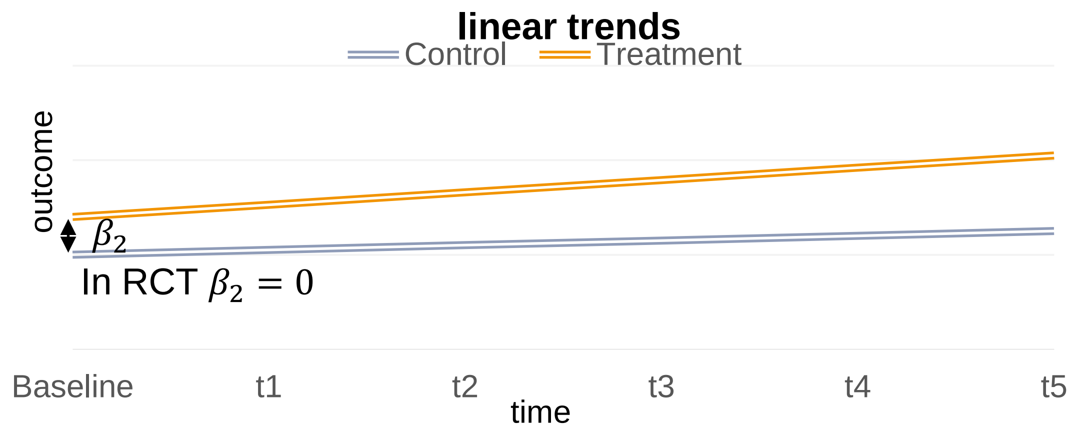
$$i = 1, .., n; j = 0, \dots, t;\ k \in \{\text{Treat; Contr}\}; \mathrm{G} \in \{F; S\}; \mathrm{N} = 2 \cdot n$$

- Possible hypotheses

$$H_0(\text{Time}): \beta_2^{\{G\}} = 0$$

$$H_0(\text{Treat}): \beta_3^{\{G\}} = 0$$

$$H_0(\text{Time} \cdot \text{Treat}): \beta_4^{\{G\}} = 0$$



- test null hypotheses $H_0: \beta_4^{\{F\}} \leq 0$ and $H_0: \beta_4^{\{S\}} \leq 0$ in a co-primary analysis, controlling the FWER using closed testing procedure [1]

[1] Marcus et al.(1976)

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Construction of Test Statistics

- Let $\mathbf{\Sigma}$ denote the covariance matrix of $\sqrt{n}(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})$ with $\mathbf{\Sigma}(4,4) = Var(\hat{\beta}_4)$ [2,3,4]

- $\mathbf{\Sigma}$ depends on model specific parameters:
  ${\sigma^{\{G\}}}^2, \rho,$ overall dropout, t

- Consider the normalized test statistics of $\hat{\beta}_4$ for F and S

$$Z^{\{F\}} = \frac{\sqrt{N} \cdot \hat{\beta}_4^{\{F\}}}{\sqrt{\Sigma^{\{F\}}(4,4)}}, \qquad Z^{\{S\}} = \frac{\sqrt{N\tau} \cdot \hat{\beta}_4^{\{S\}}}{\sqrt{\Sigma^{\{S\}}(4,4)}}$$

- Test intersection hypothesis assuming a bivariate normal distribution of $\left(Z^{\{F\}}, Z^{\{S\}}\right)'$ [5]

$$F_{H_0} = \begin{pmatrix} Z^{\{F\}} \\ Z^{\{S\}} \end{pmatrix} \overset{H_0: \beta_4^{\{F \cap S\}}}{\sim} MN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sqrt{\tau} \\ \sqrt{\tau} & 1 \end{pmatrix} \right)$$

[2] Liang and Zeger (1986)
[3] Jung and Ahn (2003)
[4] Wachtlin and Kieser (2013)
[5] Spiesens and Debois (2010)

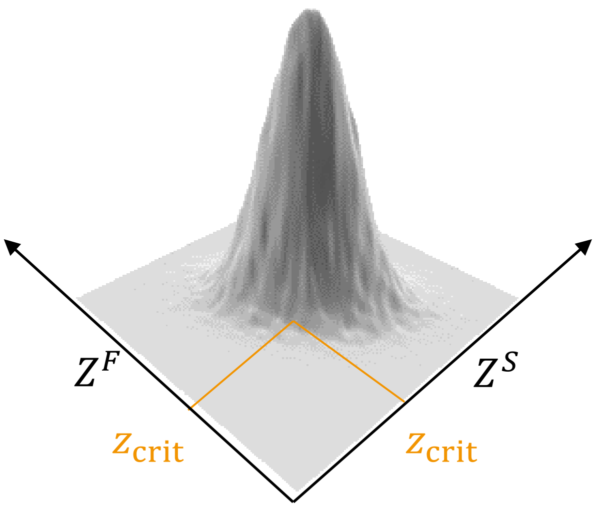
Sample Size Estimation

- Distribution under $H_1: \beta_4^{\{G\}} \geq 0$

$$F_{H_1} = \begin{pmatrix} Z^{\{F\}} \\ Z^{\{S\}} \end{pmatrix} \approx N\left(\begin{pmatrix} Z^F \\ Z^S \end{pmatrix} \middle| \begin{pmatrix} 1 & \sqrt{\tau} \\ \sqrt{\tau} & 1 \end{pmatrix} \right)$$

- Let z_{crit} denote the *equicoordinated* $\left(1 - \frac{\alpha}{2}\right)$ −quantile under H_0
- Calculate required sample size iteratively based on F_{H_1} given z_{crit}

$$N = \min\{n \mid 1 - F_{H_1}(z_{\text{crit}}) \geq Power\}$$



AED combined with Blinded Sample Size Re-estimation

Calculate initial sample size $\mathbf{N_0}$ with initial assumptions

Re-estimate nuisance parameters with pooled data and recalculate sample size

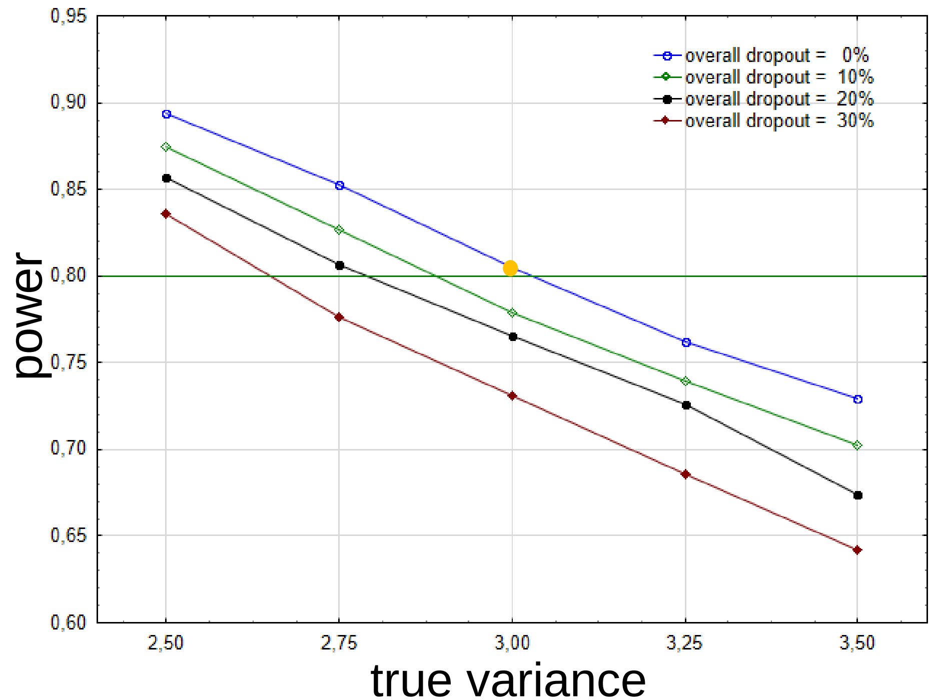
Choose to:
- continue with F
- continue with S
- stop for futility

Final analysis

Pool data over treatment/control and re-estimate
- $\sigma^{\{F\}}$, $\sigma^{\{S\}}$
- correlation ρ
- dropout

Fixed Sample Size Design

Simulations	10,000
α	0.025
$Power$	0.8
$\beta_4^{\{F\}} = \beta_4^{\{S\}}$	0.1
$\sigma_{F\backslash S}^{2^{\text{init}}} = \sigma_S^{2^{\text{init}}}$	3
τ	0.5
Overall dropout$_{init}$	0%
N_0	744

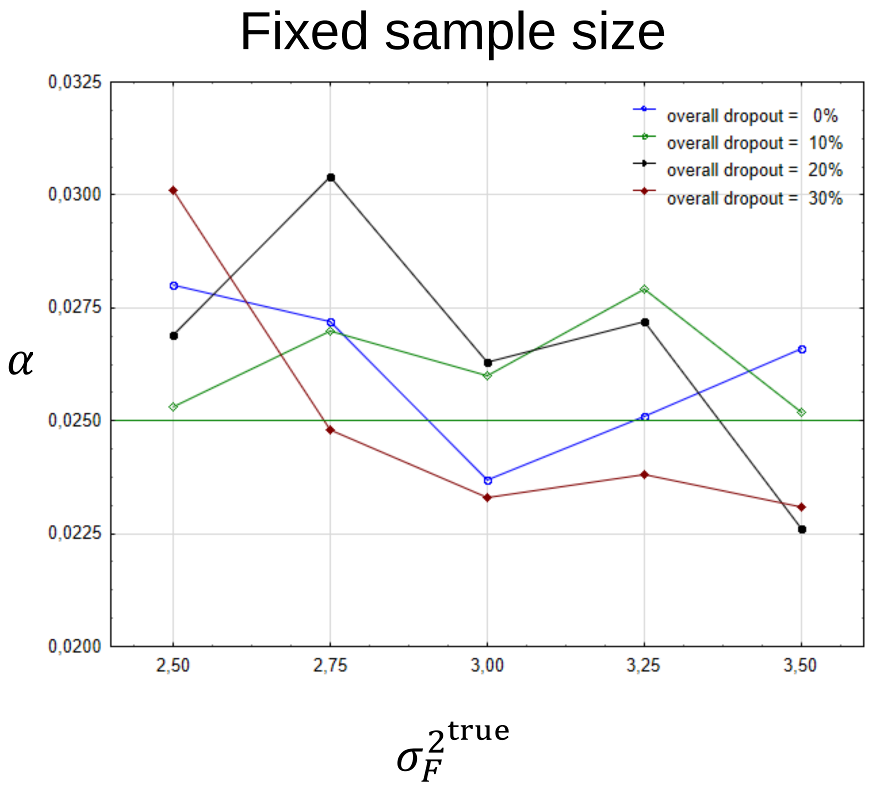


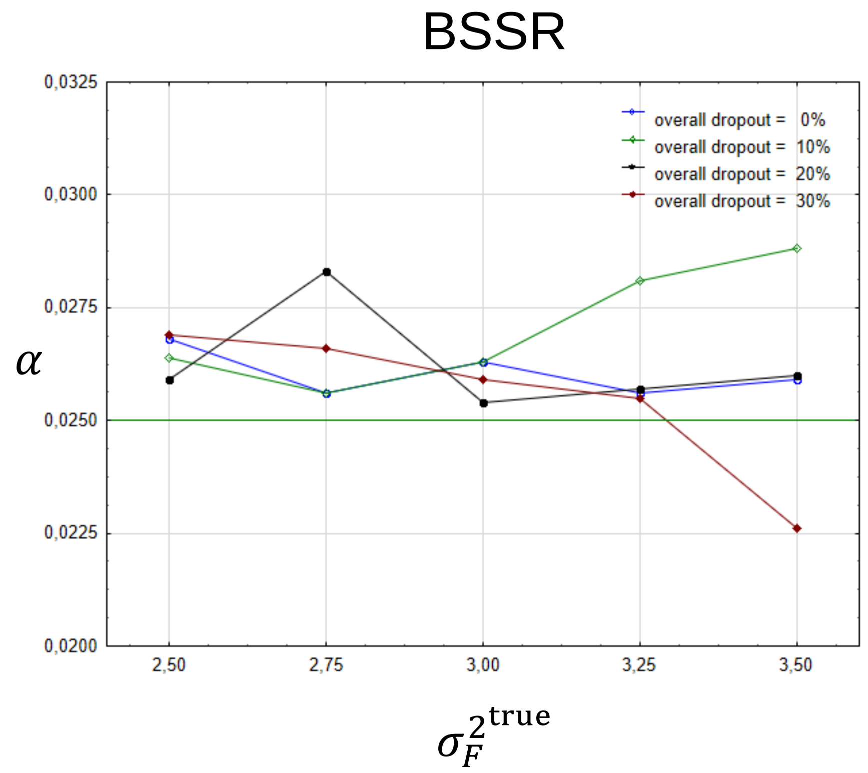
- *„The spirit behind **internal pilots** is simple: one uses patients in the pilot to alter the main study, but one does not discard those data from those patients. “* [6]

Standard values for simulation studies

Simulations	10,000
α	0.025
Power	0.8
$\beta_4^{\{F\}} = \beta_4^{\{S\}}$	0.1
$\sigma_{F\setminus S}^{2^{\text{init}}} = \sigma_S^{2^{\text{init}}}$	3
$\sigma_{F\setminus S}^{2^{\text{true}}}$	3
$\sigma_S^{2^{\text{true}}}$	(2.0, 2.5, 3.0, 3.5, 4.0)
τ	0.5
Overall dropout$_{init}$	0%
Allocation ratio	1:1
BSSR at	$0.4 \cdot N_0$
Interim at	$\max(0.4 \cdot N_0, 0.5 \cdot N_1)$
N_0	744

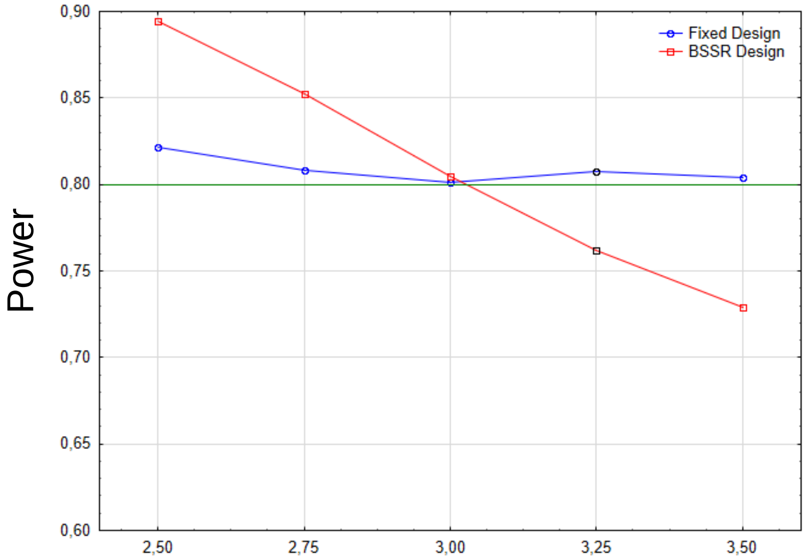
Type-I-error rate



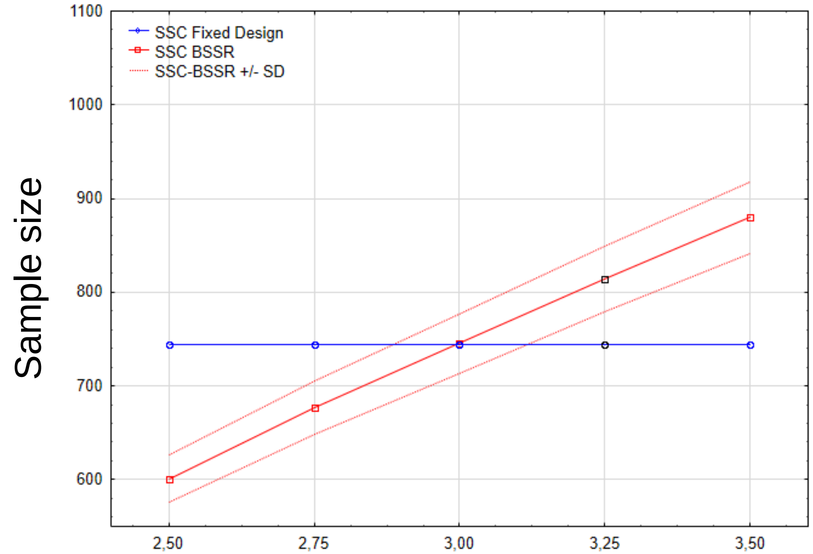


Combination of BSSR and AED

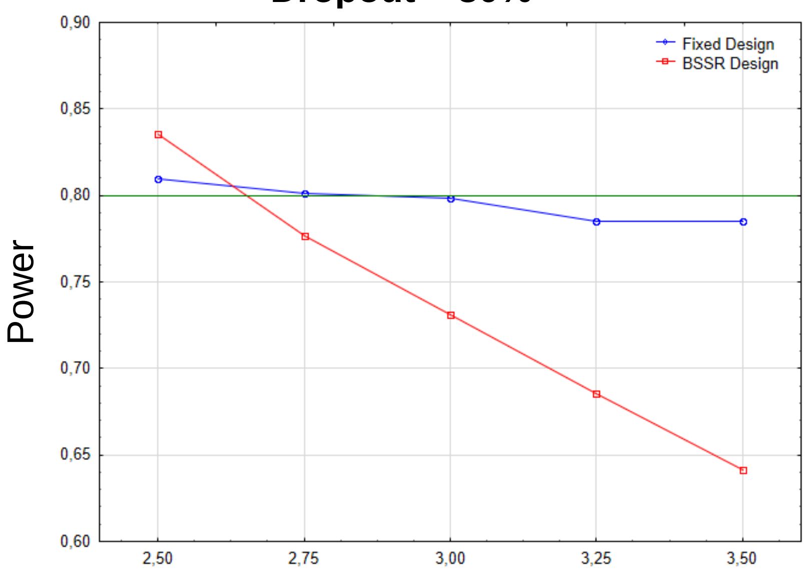
Dropout = 0%



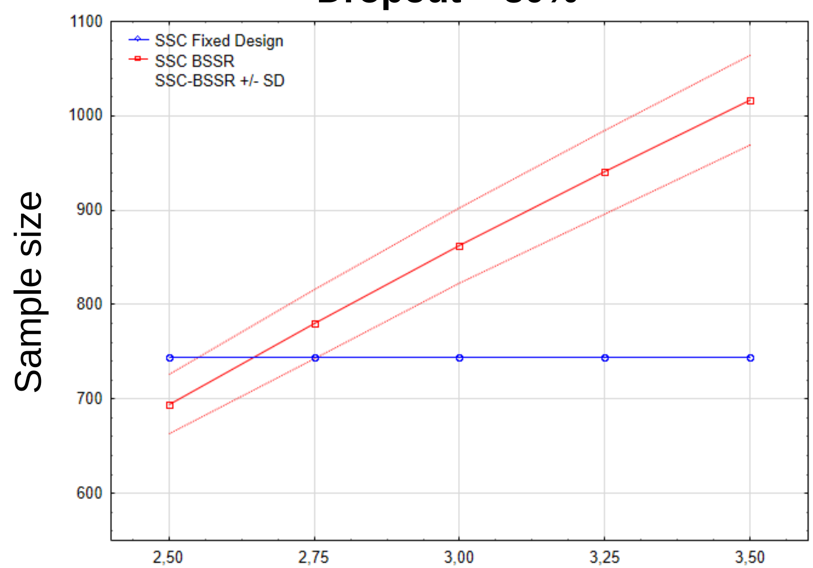
Dropout = 0%



Dropout = 30%



Dropout = 30%



Discussion & Outlook

- Combination of adaptive enrichment designs and blinded samples size re-estimation provides flexible and robust designs

- Adaptive enrichment design controls type-I-error rate

- BSSR compensates for initially miss-specified nuisance parameters and dropouts in terms of power

- Further investigate and compare weighted-GEE and MI methods in MAR situations

- Extend sample size estimation for cases where sub-population was selected in interim

For further reading

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For further reading

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Thank you for your attention!