Analysis, sample size calculation and recalculation in designs with multiple nested subgroups

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BMBF project (BundesMinisterium für Bildung und Forschung) „**BIOSTATISTISCHE METHODEN ZUR EFFIZIENTEN EVALUATION VON INDIVIDUALISIERTEN THERAPIEN (BIMIT)“.**

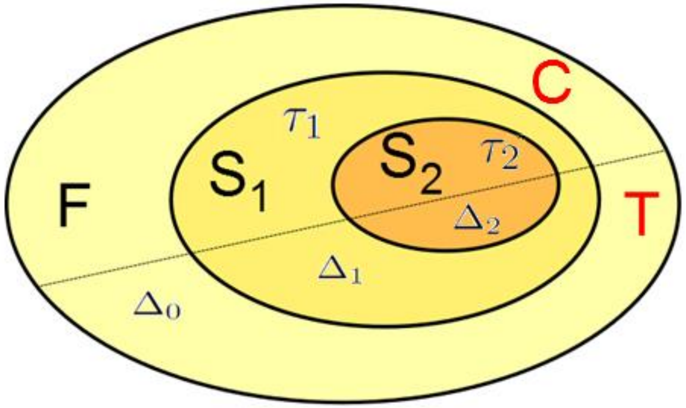
Multiple Nested Subgroups

Consider the following design

- Full population with k nested subgroups $F = S_0 \supset S_1 \cdots \supset S_k$
- Prevalences $\tau_1, \ldots, \tau_k$
  and treatment effects $\Delta_0, \ldots, \Delta_k$
- Assume

$$X_{ij1} \sim \mathcal{N}(0, \sigma^2_{S_i}),\ i = 0, \ldots, k,\ j = 1, \ldots, n^{S_i}$$ (control group)

$$X_{ij2} \sim \mathcal{N}(\Delta'_i, \sigma^2_{S_i}),\ i = 0, \ldots, k,\ j = 1, \ldots, n^{S_i}$$ (treatment group)



Analysis (fixed design)

Hypotheses and test statistics

- individual hypotheses $H_0^{\{F\}}: \Delta_0 = 0$ (no effect in full population)

  $H_0^{\{S_i\}}: \Delta_i = 0,\ i = 1, \ldots, k$ (no effect in subpopulation i)

- intersection hypotheses $H_0^{\bigcap_{i\in I} S_i}: \Delta_i = 0\ \forall i \in I \subseteq \{0, \ldots, k\}$

- standardized test statistics

$$Z^{\{F\}} = \sqrt{\frac{n}{2}}\frac{\bar{X}_F^T - \bar{X}_F^C}{\hat{\sigma}_F}$$

$$Z^{\{S_i\}} = \sqrt{\frac{n\hat{\tau}_i}{2}}\frac{\bar{X}_{S_i}^T - \bar{X}_{S_i}^C}{\hat{\sigma}_{S_i}},\ i = 1, \ldots, k$$

with $$\bar{X}_{S_i}^r = \frac{1}{\sum_{j\geq i} n^{S_j}} \sum_{j\geq i} \sum_{k=1}^{n^{S_j}} X_{jk}^r,\ r \in \{T, C\}$$

Analysis (fixed design)

- Test intersection hypotheses using the joint distribution of the standardized test statistics
  - Spiessens and Debois, 2010: normal distributed standardized test statistics with known variances
- Joint distribution? What do we know about the variances?
- **Case 1: known variances** (widely used in publications)
  - Replace $\hat{\sigma}_{S_i}$ with σ_{S_i} in the standardized test statistics
  - Then we know that under the intersection hypothesis, e.g. for only one subgroup, $H_0^{\{F,S\}}$:

$$\begin{pmatrix} Z^{\{F\}} \\ Z^{\{S\}} \end{pmatrix} \sim MN\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sqrt{\tau} \\ \sqrt{\tau} & 1 \end{pmatrix}\right)$$

Analysis (fixed design)

- **Case 2: Unknown but same variances** across subpopulations

$$\sigma = \sigma_F = \sigma_{S_1} = \cdots = \sigma_{S_k}$$

  - Then we have to estimate only one variance $\hat{\sigma}$ and replace $\hat{\sigma}_{S_i} = \hat{\sigma}$ in the standardized test statistics
  - One can show that the joint distribution is a multivariate t-distribution
    - degrees of freedom depending on the number of subjects used to estimate the variance
  - e.g. under the global intersection hypthesis $H_0^{\{\cap_{i=0}^k S_i\}}$

$$\boldsymbol{Z} = \begin{pmatrix} Z^{\{F\}} \\ Z^{\{S_1\}} \\ \vdots \\ Z^{\{S_k\}} \end{pmatrix} = \begin{pmatrix} \sqrt{\frac{n}{2}} \frac{\hat{\Delta}_F}{\hat{\sigma}} \\ \vdots \\ \sqrt{\frac{\tau_k n}{2}} \frac{\hat{\Delta}_{S_k}}{\hat{\sigma}} \end{pmatrix} \sim MT_{2(n-k-1)}(\mathbf{0}, \boldsymbol{\Sigma})$$

Analysis (fixed design)

$$\Sigma = \begin{pmatrix} 1 & \frac{\sqrt{\tau_1}\sigma_{S_1}}{\sigma_F} & \frac{\sqrt{\tau_2}\sigma_{S_2}}{\sigma_F} & \frac{\sqrt{\tau_3}\sigma_{S_3}}{\sigma_F} & \cdots & \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sigma_F} \\ \frac{\sqrt{\tau_1}\sigma_{S_1}}{\sigma_F} & 1 & \frac{\sqrt{\tau_2}\sigma_{S_2}}{\sqrt{\tau_1}\sigma_{S_1}} & \frac{\sqrt{\tau_3}\sigma_{S_3}}{\sqrt{\tau_1}\sigma_{S_1}} & \cdots & \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sqrt{\tau_1}\sigma_{S_1}} \\ \frac{\sqrt{\tau_2}\sigma_{S_2}}{\sigma_F} & \frac{\sqrt{\tau_2}\sigma_{S_2}}{\sqrt{\tau_1}\sigma_{S_1}} & 1 & \frac{\sqrt{\tau_3}\sigma_{S_3}}{\sqrt{\tau_2}\sigma_{S_2}} & \cdots & \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sqrt{\tau_2}\sigma_{S_2}} \\ \frac{\sqrt{\tau_3}\sigma_{S_3}}{\sigma_F} & \frac{\sqrt{\tau_3}\sigma_{S_3}}{\sqrt{\tau_1}\sigma_{S_1}} & \frac{\sqrt{\tau_3}\sigma_{S_3}}{\sqrt{\tau_2}\sigma_{S_2}} & 1 & \ddots & \vdots \\ \vdots & \vdots & \vdots & \ddots & \ddots & \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sqrt{\tau_{k-1}}\sigma_{S_{k-1}}} \\ \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sigma_F} & \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sqrt{\tau_1}\sigma_{S_1}} & \cdots & \cdots & \frac{\sqrt{\tau_k}\sigma_{S_k}}{\sqrt{\tau_{k-1}}\sigma_{S_{k-1}}} & 1 \end{pmatrix}$$

- **Case 3: Unknown and unequal variances**
  - Here we only have an asymptotic result, namely

under $H_0^{\{\cap_{i=0}^{k} S_i\}}$,

$$\boldsymbol{Z} = \begin{pmatrix} Z^{\{F\}} \\ Z^{\{S_1\}} \\ \vdots \\ Z^{\{S_k\}} \end{pmatrix} = \begin{pmatrix} \sqrt{\frac{n}{2}}\frac{\hat{\Delta}_F}{\hat{\sigma}_F} \\ \vdots \\ \sqrt{\frac{\tau_k n}{2}}\frac{\hat{\Delta}_{S_k}}{\hat{\sigma}_{S_k}} \end{pmatrix} \dot{\sim} \mathcal{N}(\boldsymbol{0}, \boldsymbol{\Sigma})$$

with covariance matrix as described above

Analysis (fixed design)

Case 3: Unknown and unequal variances

- Try to approximate the joint distribution by a multivariate t-distribution
  - How to choose the degrees of freedom?
  - E.g. in the case of only one subgroup: under $H_0^{\{F,S\}}$ (k=1)

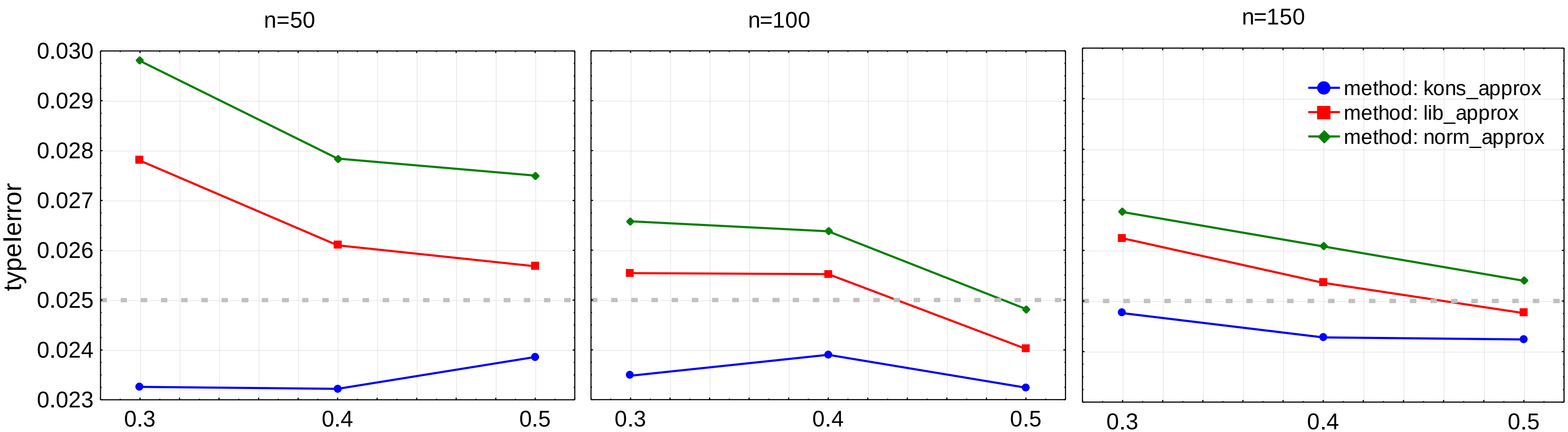
$$\begin{pmatrix} Z^F \\ Z^S \end{pmatrix} = \begin{pmatrix} \sqrt{\frac{n}{2}}\frac{\hat{\Delta}_F}{\hat{\sigma}_F} \\ \sqrt{\frac{n^S}{2}}\frac{\hat{\Delta}_S}{\hat{\sigma}_S} \end{pmatrix} \dot{\sim} MT_{df}\left(\mathbf{0}, \mathbf{\Sigma}\right)$$

  - Choose df of the full population $df = 2n - 4$ for a more liberal, or of the smallest subpopulation $df = 2n^S - 2$ for a more conservative approximation

Analysis (fixed design)

Simulations – unknown, unequal variances – t-approximation

- Type-I-error rates, $\sigma_F = 1,\ \sigma_S = 1.3$, $n_{sim} = 100,000$



prevalence of the subgroup τ

Sample Size Calculation

- under the alternative

$$Z \sim MN(\boldsymbol{\delta}, \boldsymbol{\Sigma}) \quad \text{(known variances)}$$

$$Z \sim MT_{2n-4}(\underset{\sim}{\boldsymbol{\delta}}, \widetilde{\boldsymbol{\Sigma}}) \quad \text{(unknown, same variances)}$$

$$Z \mathrel{\dot{\sim}} MT_{df}(\boldsymbol{\delta}, \widetilde{\boldsymbol{\Sigma}}) \quad \text{(unknown, unequal variances)}$$

$$df \in \{2n-4, 2n^S-2\}$$

with $\boldsymbol{\delta} = \begin{pmatrix} \sqrt{\frac{n}{2}}\frac{\Delta_F}{\sigma_F} \\ \sqrt{\frac{n_T}{2}}\frac{\Delta_S}{\sigma_S} \end{pmatrix}$

- let $G_{MT_{df}(\boldsymbol{\delta},\widetilde{\boldsymbol{\Sigma}})}$ denote the distribution function of $MT_{df}(\boldsymbol{\delta}, \widetilde{\boldsymbol{\Sigma}})$ and

$z_{MT_{df}(\mathbf{0},\boldsymbol{\Sigma}),1-\alpha}$ the $(1-\alpha)$ - equicoordinate quantile of $MT_{df}(\mathbf{0}, \boldsymbol{\Sigma})$

- use estimates of nuisance parameters and effect sizes, e.g. based on previous studies, to calculate the initial sample size via

$$N_{init} = \min\ n,\ \text{s.t.}\ 1 - G_{MT_{df}(\boldsymbol{\delta},\widetilde{\boldsymbol{\Sigma}})}\left(z_{MT_{df}(\mathbf{0},\boldsymbol{\Sigma}),1-\alpha}\right) \geq 1-\beta$$

Sample Size Calculation

- In the case of unknown, unequal variances one has to choose which df to use for the MT-distribution in the final analysis and in the sample size calculation
- Calculating the sample size via a multivariate T-distribution requires to calculate a new equicoordinate quantile in each step of the search algorithm
    - Using the MN-distribution only one quantile is calculated
- Sample size calculation heavily depends on estimates of the nuisance parameters $\hat{\sigma}_F, \hat{\sigma}_{S_1}, \ldots, \hat{\sigma}_{S_k}$
  $\hat{\tau}_1, \ldots, \hat{\tau}_k$
- Multivariate Normal and t Probabilities, see Genz and Bretz (2009)
    - R package multcomp

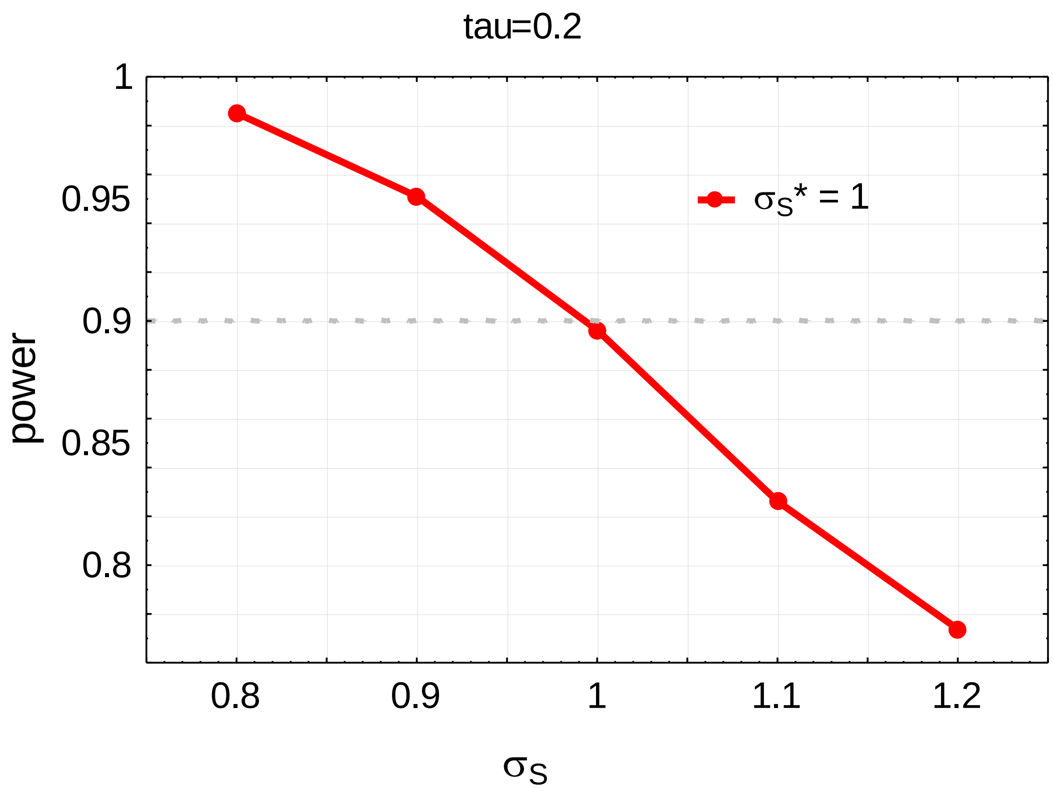
Sample Size Calculation - Performance

- Misspecification of the nuisance parameters can lead to substantial under/over estimation of the sample size

$n_{sim} = 10,000$

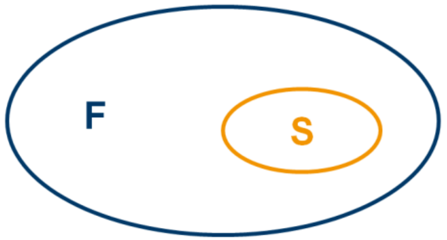
$\Delta_S = 1$

$1-\beta = 0.9$



- Solution: Internal Pilot Study Design (Wittes & Brittain, 1990)

IPS design with Blinded Review



- here: nuisance parameters

$$\sigma^2_F, \sigma^2_{S_1}, \ldots, \sigma^2_{S_k}$$
$$\tau_1, \tau_2, \ldots, \tau_k$$

- after n_1=p* N_0 subjects per group (treatment/control):
  - blinded reestimation via „lumped variance“

$$\widehat{\sigma}^2_F = \widehat{\sigma}^2 = \frac{1}{2n_1 - 1} \sum_{i=0}^{k} \sum_{j=1}^{n_1^{S_i}} \sum_{l=1}^{2} (X_{ijl} - \bar{X}_{i..})^2$$

$$\widehat{\sigma}^2_{S_i} = \frac{1}{2n_1^{S_i} - 1} \sum_{s=i}^{k} \sum_{j=1}^{n_1^{S_l}} \sum_{l=1}^{2} (X_{sjl} - \bar{X}_{s..})^2, \; i = 1, \ldots, k$$

  - Prevalences

$$\widehat{\tau}_i = \frac{n_1^{S_i}}{n_1}, \; i = 1, \ldots, k$$

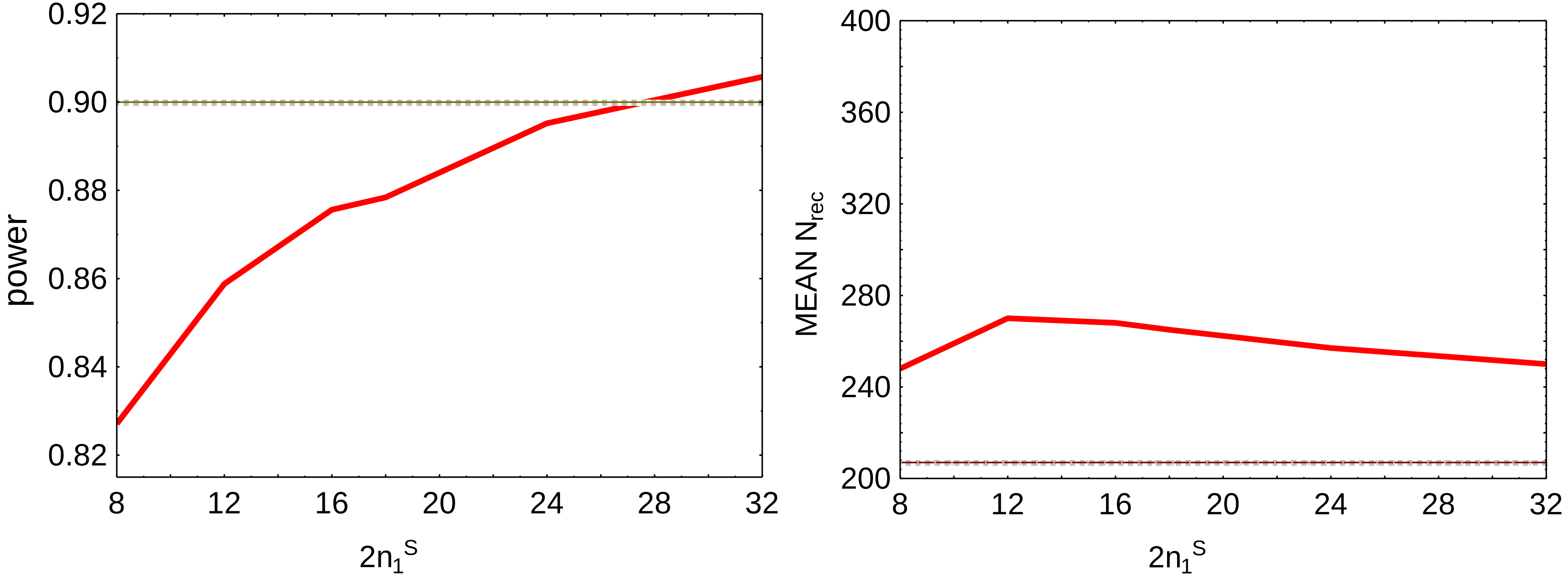
  - plug in the new nuisance parameter estimates in the sample size calculation method

BSSR - Simulations

- Simulated power and corresponding recalculated sample sizes depending on the number of subjects in the subgroup at the timepoint of the blinded review

$1-\beta = 0.9 \qquad \Delta_S = 1 \qquad \sigma_S^* \neq \sigma_S \qquad n_{sim} = 10,000$

- Conservative approximation $df = 2n^S - 2$



Blinded Sample Size Reestimation

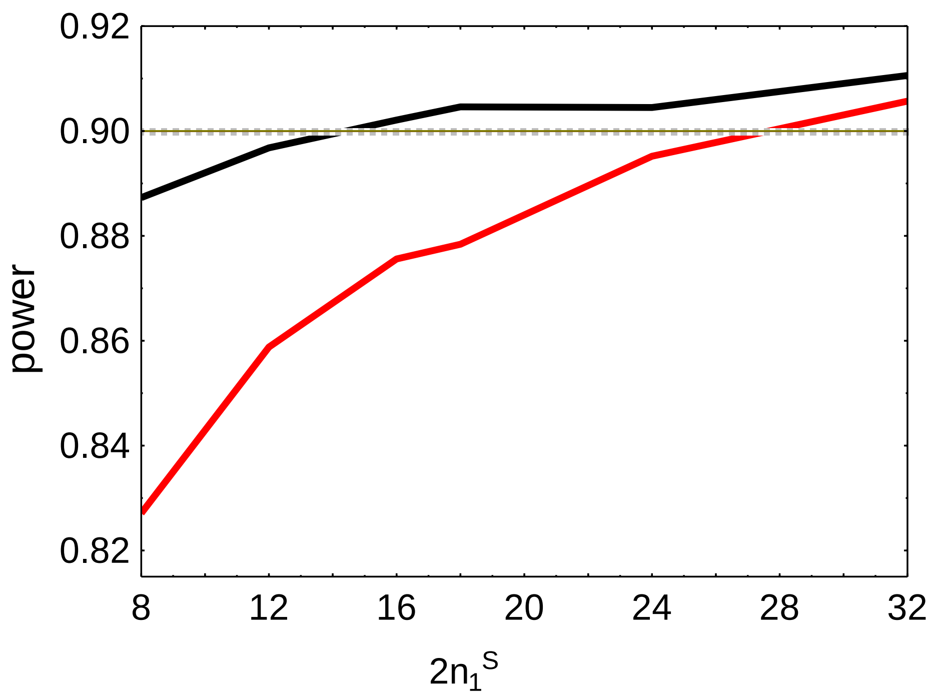
- minimal number of subjects in the smallest subgroup to get an appropriate approximation
- when plugging in the new nuisance parameter estimates, we use the same search algorithm to determine the new sample size
  - Zucker et. al (1999): use df dependent on the number of subjects at the blinded review
  - Here: try to use df depending on n_1^S to improve when dealing with small subgroups

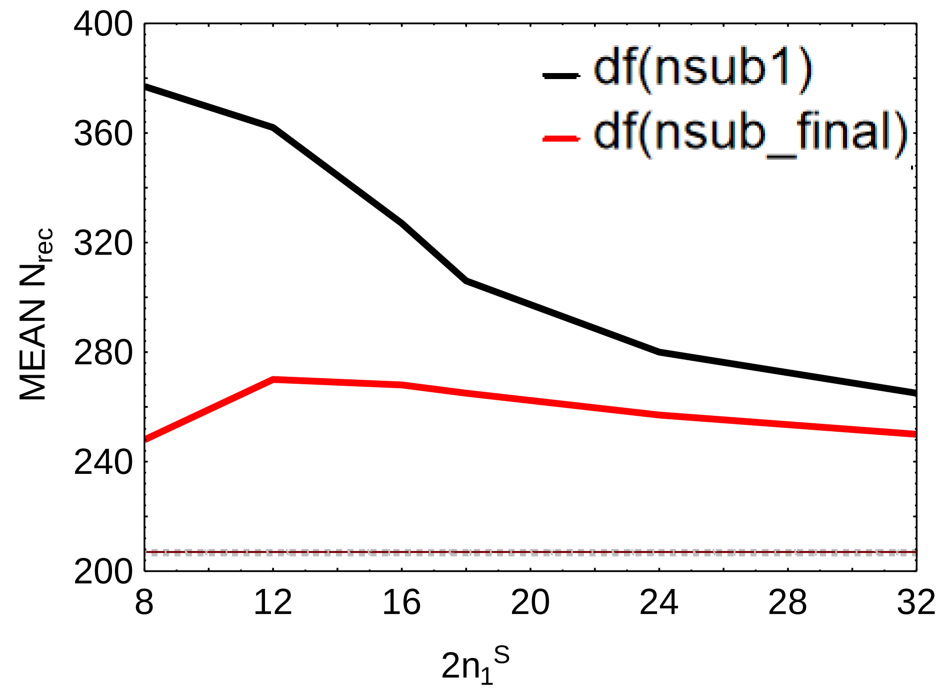
BSSR - Simulations

- Simulated power and corresponding recalculated sample sizes depending on the number of subjects in the subgroup at the timepoint of the blinded review

$1-\beta = 0.9 \qquad \Delta_S = 1 \qquad \sigma_S^* \neq \sigma_S \qquad n_{sim} = 10,000$

- Conservative approximation at final analysis





Conclusions & Discussion

- Method to analyze multiple nested supgroup designs via joined distribution of standardized test statistics
- Approximation for unknown and unequal variances in the subgroups
- Sample size calculation approach derived using this approx requires minimum 20-30 subjects in smallest subgroup
  - compare Sandvik et. al (1996)
- R package in work
- Next step: use these findings in the combination of BSSR and Adaptive Enrichment Methods

References

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