Model-based statistical approaches for pharmacokinetic bioequivalence studies with sparse sampling and extension to two-stage designs

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Evaluation of Model-Based BioEquivalence (MBBE) statistical approaches for sparse designs PK studies

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

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  Simulation study
  Results

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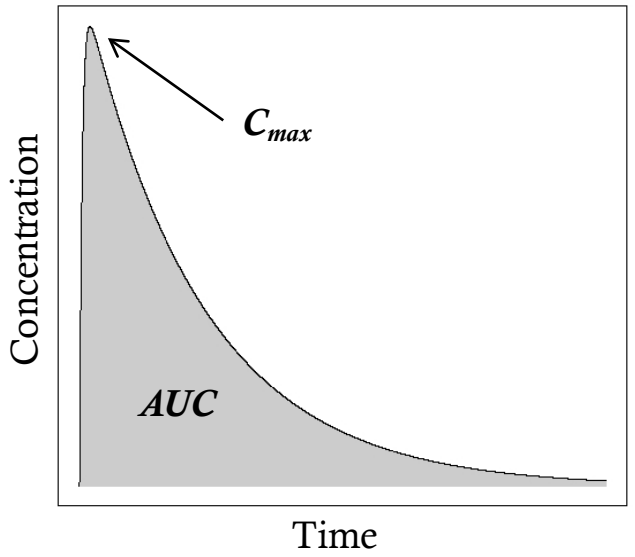
Introduction

- Pharmacokinetic (PK): study of the time course of the drug in the body[1]
  - AUC: area under the plasma drug concentration versus time curve
  - C_{max}: maximum plasma concentration



- Bioequivalence (BE): PK equivalence between drug formulations
  - traditionally, TOST[2] on estimates of AUC and C_{max} obtained using the non-compartmental analysis (NCA)[3]
  - in a previous work, model-based (MB) TOST, using nonlinear mixed effects model (NLMEM), was proposed as an alternative for NCA-based TOST in sparse design[4]
- At the design stage
  - assumptions on the expected variability of AUC and C_{max} are needed
  - if uncertainty, recently proposed to perform two-stage studies for TOST-NCA: group sequential[5] or adaptive designs[6]

[1]: J. Gabrielsson *et al., Pharmacokinetic & pharmacodynamic,* 4th edition 2006
[2]: Schuirmann, *Journal of Pharmacokinetics and Biopharmaceutics*, 1987
[3]: Guidance for industry – Bioequivalence: Blood level bioequivalence study, VICH GL52, 2016
[4]: Dubois *et al., Statistics in Medicine*, 2011
[5]: Kieser *et al., Statistics in Medicine*, 2015
[6]: Maurer *et al., Statistics in Medicine*, 2018

Two one-sided test (TOST)

- β^{Tr}: ratio of AUC or C_{max} geometric means to be compared to the threshold $\delta = \log(1.25) \approx 0.223$[1]
- TOST null hypothesis $H_0: \{\beta^{Tr} \leq -\delta \text{ or } \beta^{Tr} \geq \delta\}$ is decomposed into

$$H_{0,-\delta}: \{\beta^{Tr} \leq -\delta\} \text{ or } H_{0,\delta}: \{\beta^{Tr} \geq \delta\}$$

- both $H_{0,-\delta}$ and $H_{0,\delta}$ shall be rejected at $\alpha = 5\%$ if

$$Z_{-\delta} = \frac{\beta^{Tr} + \delta}{SE(\beta^{Tr})} \geq z_{1-\alpha} \text{ and } Z_{\delta} = \frac{\beta^{Tr} - \delta}{SE(\beta^{Tr})} \leq -z_{1-\alpha}$$

$SE(\beta^{Tr})$: standard error of β^{Tr}

$z_{1-\alpha}$: $1-\alpha^{th}$ quantile of the normal distribution

- or equivalently

$$CI(\beta^{Tr})_{1-2\alpha} = \beta^{Tr} \pm z_{1-\alpha} \times SE(\beta^{Tr}) \text{ included in } [-\delta ; +\delta]$$

where $CI_{1-2\alpha}(\beta^{Tr})$: confidence interval of β^{Tr} at level $1-2\alpha$

NB: Often exponential of each boundary of the $CI_{90\%}$ are computed and compared to [0.8 ; 1.25]

[1]: Guidance for industry – Bioequivalence: Blood level bioequivalence study, VICH GL52, 2016

NCA-TOST for crossover designs

- AUC and C_{max} traditionally obtained using the trapezoidal rule and directly from the observations respectively

- Estimation using linear mixed effect model

- Individual AUC of subject i=1, …, N at period k=1, …, K

$$log(AUC_{ik}) = \lambda_{AUC} + \boldsymbol{\beta_{AUC}^{Tr}} T_{ik} + \beta_{AUC}^{P} P_k + \beta_{AUC}^{S} S_i + \eta_{AUC_i} + \kappa_{AUC_{ik}}$$

  - λ_{AUC}: expected value of AUC for reference class
  - $\boldsymbol{\beta_{AUC}^{Tr}}$, β_{AUC}^{P}, β_{AUC}^{S}: treatment, period, and sequence effect coefficients
  - T_{ik}, P_k, S_i: treatment, period, and sequence covariate vectors
  - $\eta_{AUC_i} \sim N(0, \omega_{AUC})$: between-subject random effect
  - $\kappa_{AUC_{ik}} \sim N(0, \gamma_{AUC})$: within-subject random effect

  - Asymptotic $\boldsymbol{SE(\beta_{AUC}^{Tr})}$ estimated from observed Fisher Information matrix (FIM)

  - NB: Same for Cmax

NCA-TOST for crossover designs

- AUC and C_{max} traditionally obtained using the trapezoidal rule and directly from the observations respectively
- Estimation using linear mixed effect model

PROS
- Reproductible
- Few assumptions

CONS
- Require more than 10 samples per subject per period
- Not appropriate for nonlinear PK

NLMEM- TOST for crossover studies

- For crossover design, the concentration y_{ijk} of subject i $(i = 1, \dots, N)$, at sampling time t_{ijk} $(i = 1, \dots, n_{ijk})$, at period k $(k = 1, \dots, K)$

$$y_{ijk} = f(t_{ijk}, \varphi_{ik}) + g(t_{ijk}, \varphi_{ik})\epsilon_{ijk}$$

  - where
    - $f(t_{ijk}, \varphi_{ik})$: structural PK model
    - $g(t_{ijk}, \varphi_{ik}) = \sigma_{inter} + \sigma_{slope} \times f(t_{ijk}, \varphi_{ik})$: combined error model
    - $\epsilon_{ijk} \sim N(0,1)$: residual errors

$$log(\varphi_{ikl}) = log(\lambda_l) + \boldsymbol{\beta_l^{Tr}}\ Tr_i + \beta_l^P\ P_k + \beta_l^S\ S_i + \eta_{il} + \kappa_{ikl}$$

  - where
    - $l = 1, \dots, p$ with p the number of PK parameters
    - λ_l: fixed effect for the covariate reference class
    - Tr_i, P_k, S_i: indicators for the treatment, period and sequence
    - $\boldsymbol{\beta_l^{Tr}}$, β_l^P, β_l^S: coefficients of treatment, period and sequence effects on the log of the PK parameter
    - $\eta_{il} \sim N(0, \omega_{il})$: between subject variability (BSV)
    - $\kappa_{ikl} \sim N(0, \gamma_{il})$: within subject variability (WSV)
- $\beta^{Tr} = h(\lambda_l, \boldsymbol{\beta_l^{Tr}})$ on AUC and C_{max} are secondary parameters of PK model
- $SE(\beta^{Tr})$ determined by delta method using fixed effects population Fisher Information Matrix (FIM)

NLMEM- TOST for crossover studies

- For **crossover** design, the concentration y_{ijk} of subject i $(i = 1, \dots, N)$, at sampling time t_{ijk} $(i = 1, \dots, n_{ijk})$, at period k $(k = 1, \dots, K)$

$$y_{ijk} = f(t_{ijk}, \varphi_{ik}) + g(t_{ijk}, \varphi_{ik})\epsilon_{ijk}$$

$$log(\varphi_{ikl}) = log(\lambda_l) + \boldsymbol{\beta_l^{Tr}}\, Tr_i + \beta_l^P\, P_k + \beta_l^S\, S_i + \eta_{il} + \kappa_{ikl}$$

  - $\beta^{Tr} = h(\lambda_l, \boldsymbol{\beta_l^{Tr}})$ on AUC and C_{max} are secondary parameters of PK model
  - $SE(\beta^{Tr})$ determined by delta method using fixed effects population Fisher Information Matrix (FIM)

PRO
- Few samples per subject

CON
- Assumptions on PK model
- Potential increase of type I error when using asymptotic SE[1]

[1]: Dubois *et al., Statistics in Medicine*, 2011

TOST for parallel designs

- For biosimilars (long half-life) and BE studies in patients, often parallel designs are needed
- For both NCA and NLMEM, the approach is similar except
  - There is no within subject variability
  - There is not sequence and period effect

- NCA-TOST
  - Individual AUC of subject i=1,…N

$$log(AUC_i) = \lambda_{AUC} + \beta_{AUC}^{Tr} T_i + \eta_{AUC_i}$$

- NLMEM-TOST

$$log(\varphi_{il}) = log(\lambda_l) + \boldsymbol{\beta_l^{Tr}}\, Tr_i + \eta_{il}$$

Objectives

1. To propose **new approaches** to correct for type I error inflation of TOST in MBBE and to evaluate them by **clinical trial simulation**
   - Crossover designs
   - Parallel designs
2. To implement **two-stage sequential[1] and adaptive[2] designs** with model-based TOST and to evaluate them by **clinical trial simulation**

[1]: Kieser *et al.*, *Statistics in Medicine*, 2015

[2]: Maurer *et al.*, *Statistics in Medicine*, 2018

Objectives

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   - Crossover designs
   - Parallel designs
2. To implement **two-stage sequential[1] and adaptive[2] designs** with model-based TOST and to evaluate them by **CTS**

[1]: Kieser *et al.*, *Statistics in Medicine*, 2015

[2]: Maurer *et al.*, *Statistics in Medicine*, 2018

Other approaches for computing SE in MBBE

TOST using parametric bootstrap (TOST boot)

1) Build 1,…,B (B=250) data sets of $\sum_{i=1}^{N}\sum_{k=1}^{K} n_{ik}$ vectors of response using equation (1) and

- B (Np) matrices of random effects from N(0,$\hat{\Omega}$)
- B (2Np) matrices of random effects from N(0,$\hat{\Gamma}$)
- B $\sum_{i=1}^{N}\sum_{k=1}^{K} n_{ik}$ residual errors from N(0,1)

3) Fit the B new datasets to get B estimates of (λ,β,ω,γ,a,b)

4) TOST using the standard deviation of the B $\widehat{\beta_m{}^{Tr}}$ instead of SE($\widehat{\beta_m{}^{Tr}}$)

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4) TOST using the standard deviation of the B $\widehat{\beta_m{}^{Tr}}$ instead of SE($\widehat{\beta_m{}^{Tr}}$)

TOST using *a posteriori* distribution (TOST post)

1) Draw 1,…,B (B=1000) samples from the *a posteriori* distributions of (λ,β,ω,γ,a,b) using Stan

- Initialize the HMC chain at estimates from step 1
- Default distribution on fixed effects λ, β
- Cauchy(0,2.5) priors on ω, γ, a, b i.e.

3) TOST using the standard deviation of $\widehat{\beta_m{}^{Tr}}$ *a posteriori* distribution.

Other approaches for computing SE in MBBE

TOST using parametric bootstrap (TOST boot)

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3) TOST using standard deviation of $\widehat{\beta_m{}^{Tr}}$ *a posteriori* distribution.

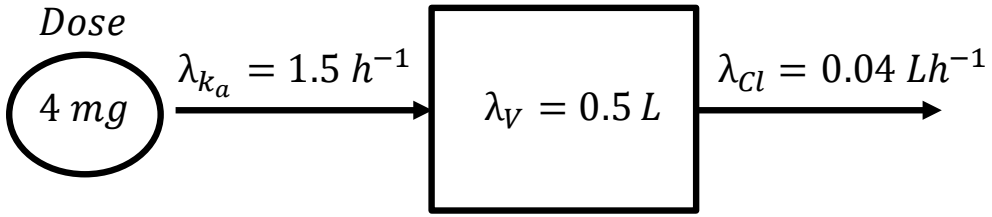
TOST using Gallant correction (TOST Gallant)

1) Calculate $SE_G(\widehat{\beta_m{}^{Tr}}) = SE(\widehat{\beta_m{}^{Tr}}) \times \sqrt{\frac{2N}{df_{Gallant}}}$ with $df_G = 2N - dim(\lambda)$

2) TOST using $SE_G\left(\widehat{\beta_m{}^{Tr}}\right)$ instead of SE($\widehat{\beta_m{}^{Tr}}$) and $t_{1-\alpha,df_G}$ instead of $z_{1-\alpha}$

Crossover design: Simulation study

- PK model concentrations of theophylline[1]



- Under rich (R) and sparse (S) designs:
  - **R**: n=10 sampling times, t =(0.25,0.5, 1,2,3.5, 5, 7, 9,12,24)
  - **S**: n=3 sampling times, t = (0.25,3.35,24)

➢ **2 designs N =40, n=10 ; N=40, n=3**

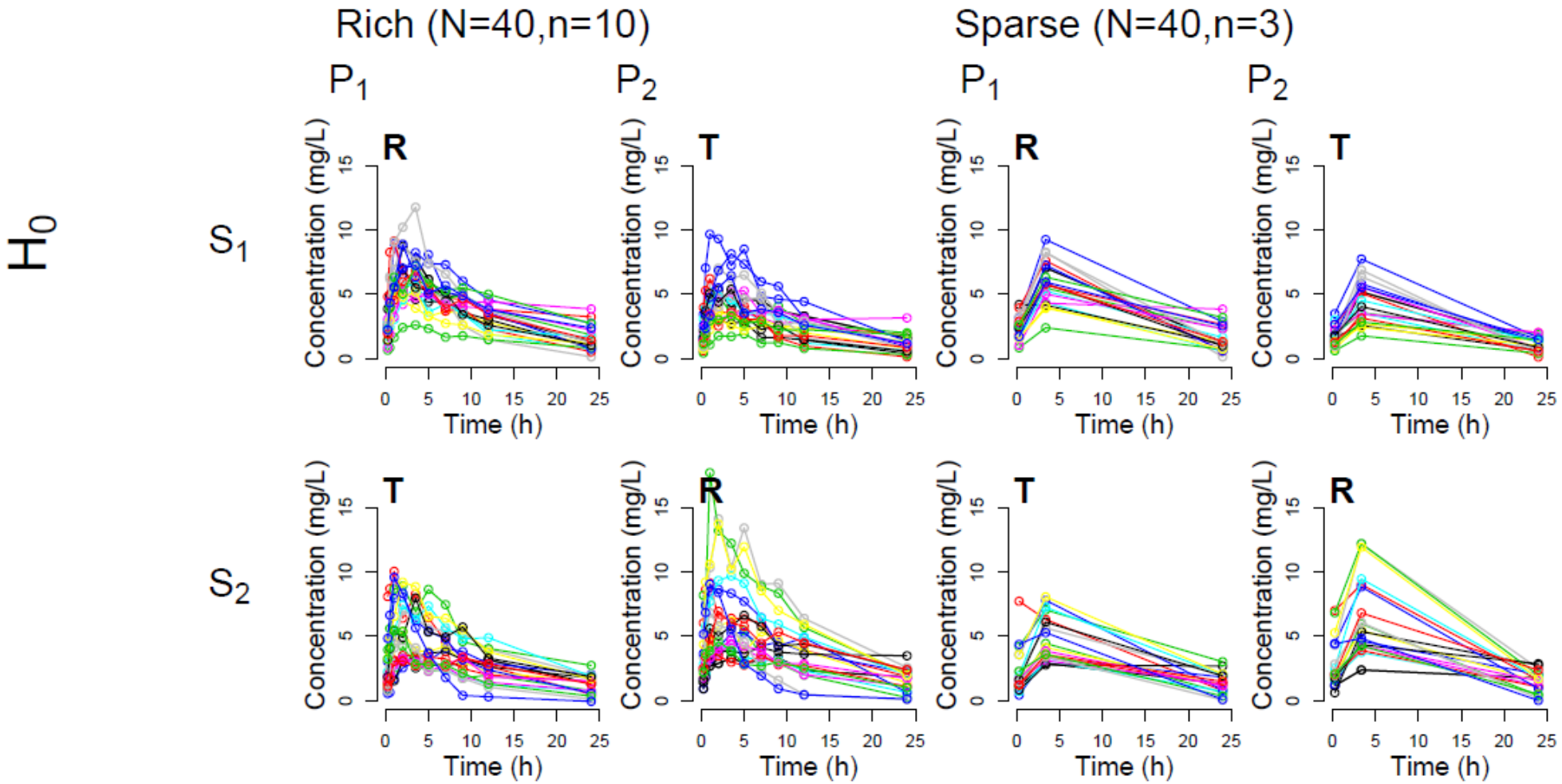
$\omega(\%)$	$\gamma(\%)$	σ_{inter} (mg/L)	σ_{slope} (%)
50	15	0.1	10

Same ω and γ for all PK parameters
$\beta^P = \beta^S = 0$

- Simulations under H_0: $\beta^{Tr} = \log(0.80)$ and H_1: $\beta^{Tr} = \log(1) = 0$
- Evaluation of BE on $\boldsymbol{AUC}$ and $\boldsymbol{C_{max}}$ independently
- 500 data sets
- **Estimation using SAEM algorithm in Monolix software**

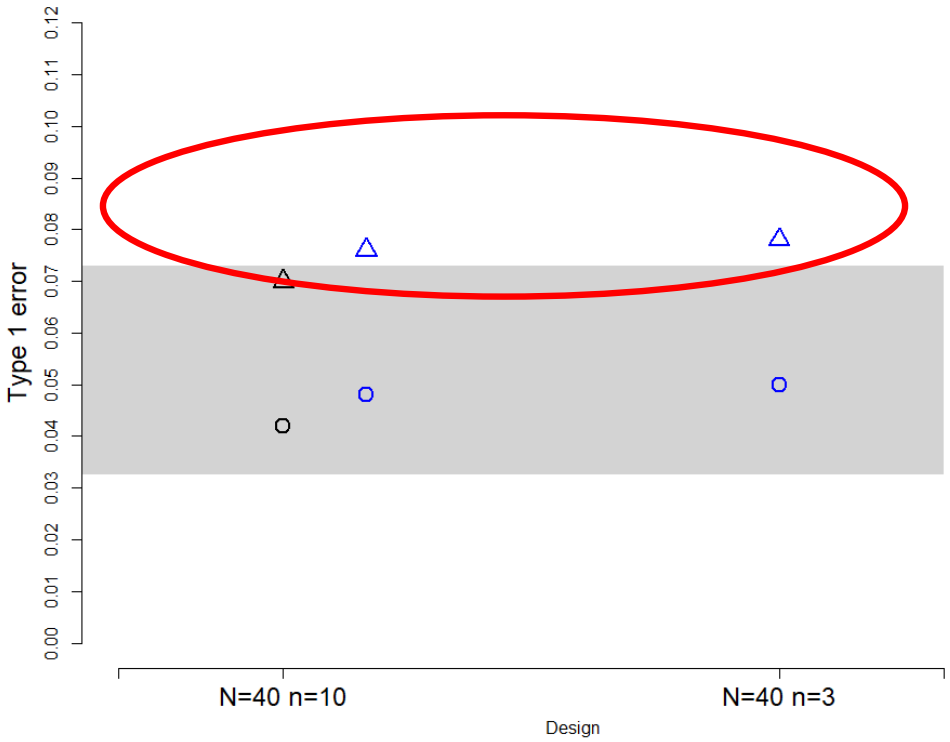
[1]: Dubois *et al., Statistics in Medicine*, 2011

Crossover design: One simulated data set



Crossover: type I error with asymptotic SE

Type I error and Power of **NCA TOST** and **MB TOST**
on β_{AUC}^{Tr} (**o**) and β_{Cmax}^{Tr} (**Δ**)

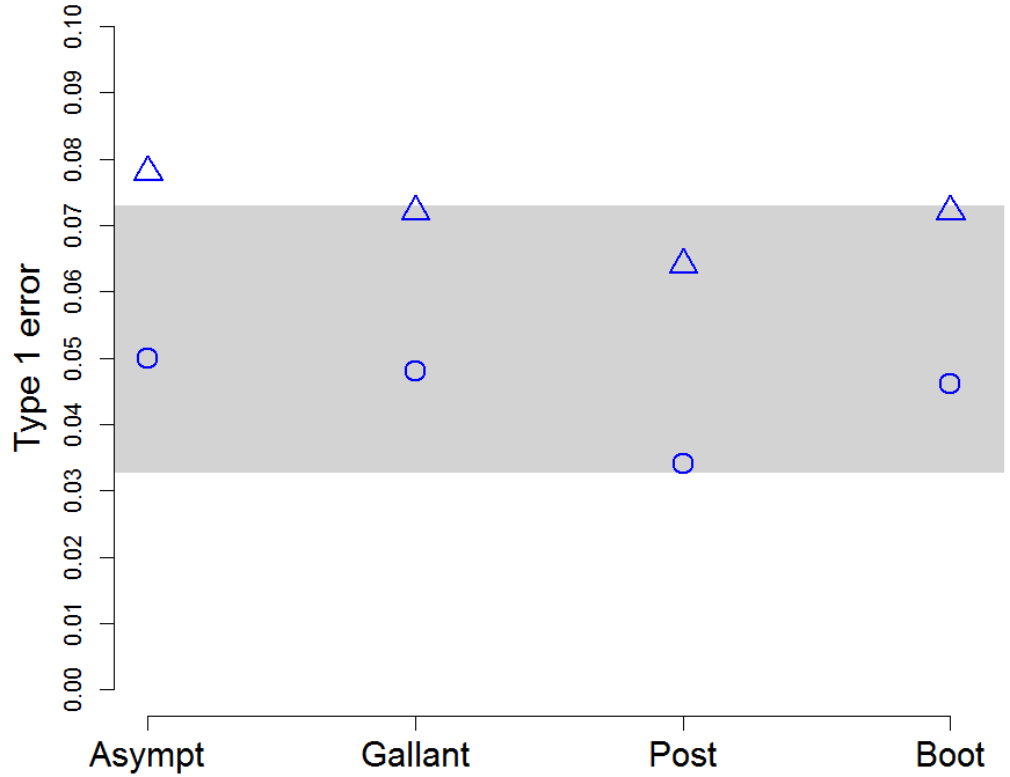


Power	N=40, n=10		N=40 , n=3
	NCA TOST	**MB TOST Asympt**	**MB TOST Asympt**
β_{AUC}^{Tr}	**1.000**	**1.000**	**0.998**
β_{Cmax}^{Tr}	**1.000**	**1.000**	**1.000**

Crossover: results for various SE

Type I error and Power of **MB TOST** on β_{AUC}^{Tr} (**o**) and β_{Cmax}^{Tr} (**Δ**)

N=40 n=3

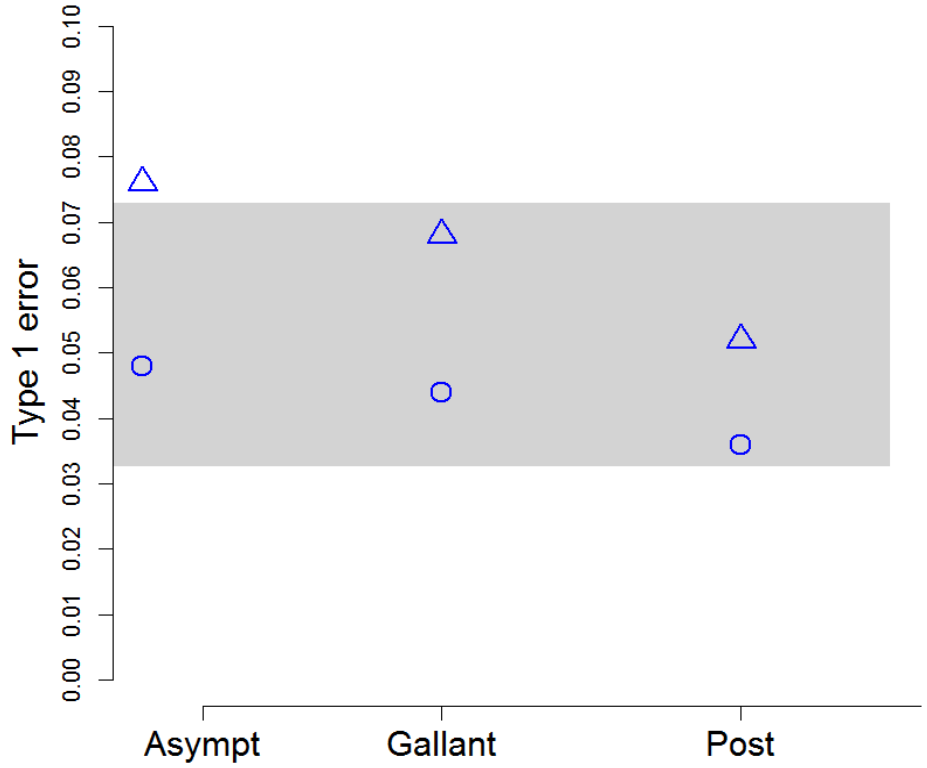


	1 min	1 min	2.5 min	5 hours
β_{AUC}^{Tr}	0.998	0.998	0.996	*
β_{Cmax}^{Tr}	1.000	1.000	0.996	*

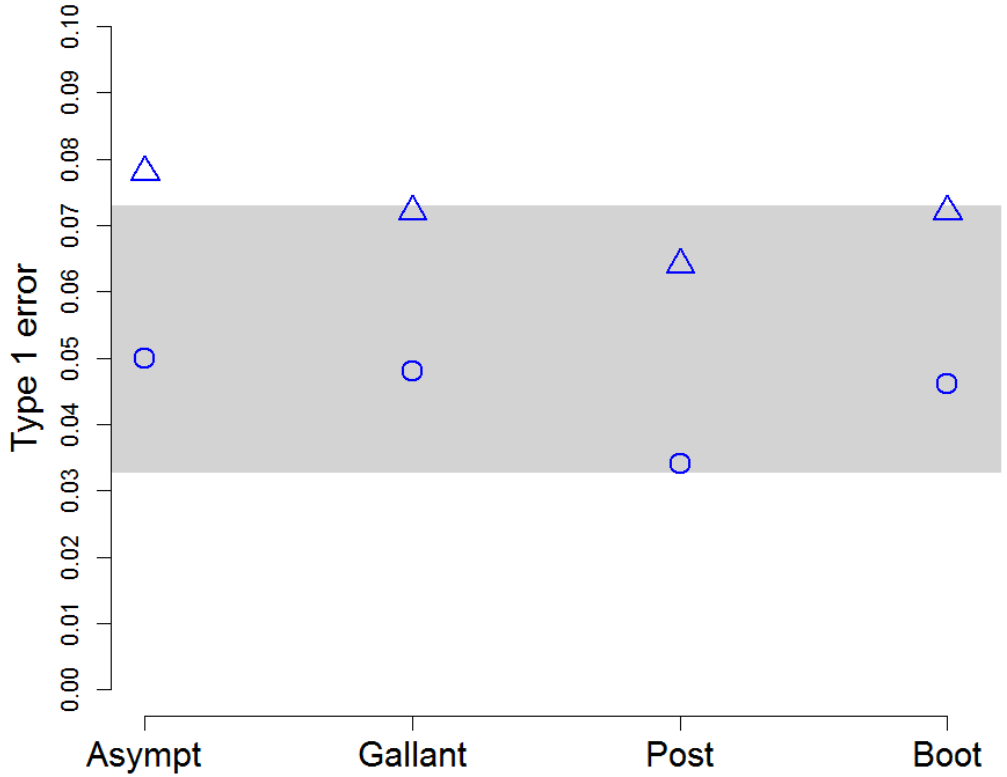
Crossover: results for various SE

Type I error and Power of **MB TOST** on β_{AUC}^{Tr} (**o**) and β_{Cmax}^{Tr} (**Δ**)

N=40 n=10



N=40 n=3



Computing time	1 min	1 min	7 min

	1 min	1 min	2.5 min	5 hours

Power				
β_{AUC}^{Tr}	1.000	1.000	0.998	
β_{Cmax}^{Tr}	1.000	1.000	0.998	

β_{AUC}^{Tr}	0.998	0.998	0.996	*
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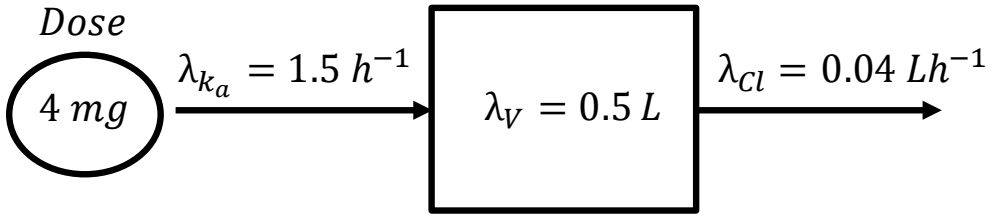
Parallel design: Simulation study

- PK model concentrations of theophylline[1]



- Under rich (R) and sparse (S) designs:
  - **R**: n=10 sampling times, t =(0.25,0.5, 1,2,3.5, 5, 7, 9,12,24)
  - **S**: n=3 sampling times, t = (0.25,3.35,24)

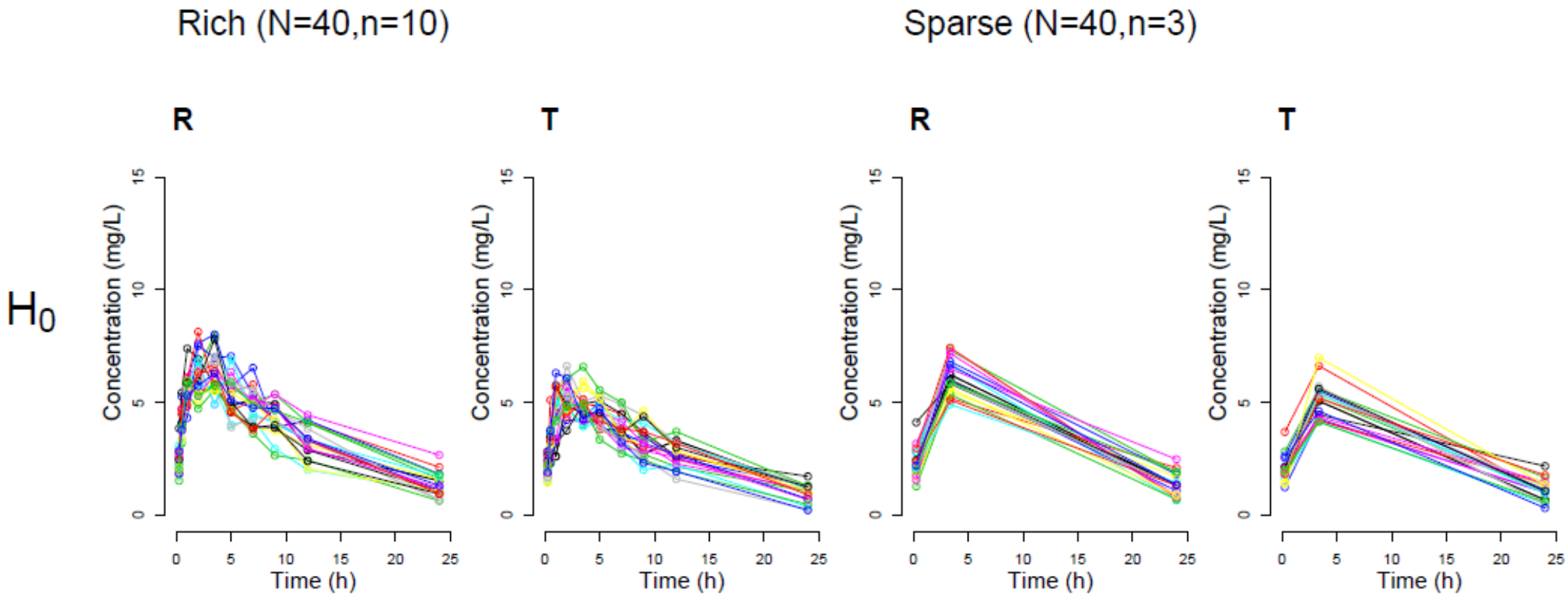
- **2 designs: N =40, n=10; N=40, n=3 (N= 20 per group)**
- **2 levels of variability**

	ω_{Ka} (%)	ω_V (%)	ω_{Cl} (%)
Low (**L**)	22	11	22
High (**H**)	52		

- Simulations under H_0: $\beta^{Tr} = \log(0.80)$ and H_1: $\beta^{Tr} = \log(1) = 0$
- Evaluation of BE on $\boldsymbol{AUC}$ and C_{max} independently
- 500 data sets
- **Estimation using SAEM algorithm in saemix (R)**

[1]: Dubois *et al., Statistics in Medicine*, 2011

Parallel design: One simulated data set for low variability



[1]: Dubois *et al., Statistics in Medicine*, 2011

Parallel: type I error of TOST with asymptotic SE

Sampling time		Rich		Sparse	
Variability		Low	High	Low	High
NCA-TOST	AUC	0.052	**0.022**	-	-
	C_{max}	0.062	**0.012**	-	-
MB-TOST	AUC	0.056	**0.004**	**0.076**	**0.006**
	C_{max}	0.058	**0.008**	0.066	**0.002**

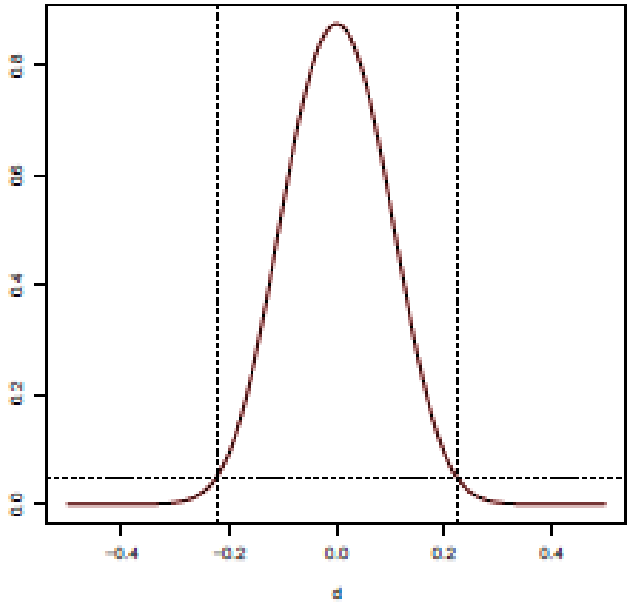
TOST and BOT

- **TOST is a conservative test in case of high variability** [1,2]
- **Better test in BE: the Bioequivalence Optimal Test (BOT)**
- **TOST on $\boldsymbol{\beta^{Tr}}$**
  - Both $H_{0,-\delta}: \{\beta^{Tr} \leq -\delta\}$ and $H_{0,\delta}: \{\beta^{Tr} \geq \delta\}$ shall be rejected at $\alpha = 5\%$
  - Reject if: $\frac{\beta^{Tr}}{SE(\beta^{Tr})} \geq z_{1-\alpha} - \frac{\delta}{SE(\beta^{Tr})}$ and $\frac{\beta^{Tr}}{SE(\beta^{Tr})} \leq -z_{1-\alpha} + \frac{\delta}{SE(\beta^{Tr})}$
  - ➢ Implies $SE(\beta^{Tr}) > \frac{\delta}{z_{1-\alpha}}$ otherwise type I error of TOST = 0
- **BOT on $\boldsymbol{\beta^{Tr}}$**
  - Idea: the distribution of the absolute difference of the treatment effects on log AUC/log Cmax are given by a folded normal distribution
  - **Reject if: $\left|\boldsymbol{\beta^{Tr}}\right| \leq \boldsymbol{u_\alpha}$ where $\boldsymbol{u_\alpha}$ is the $\boldsymbol{\alpha}$-quantile of the folded normal distribution $\boldsymbol{N_F(\delta, SE(\beta^{Tr})^2)}$**
  - ➢ Type I error is α per construction
  - ➢ BOT is uniformly most powerful

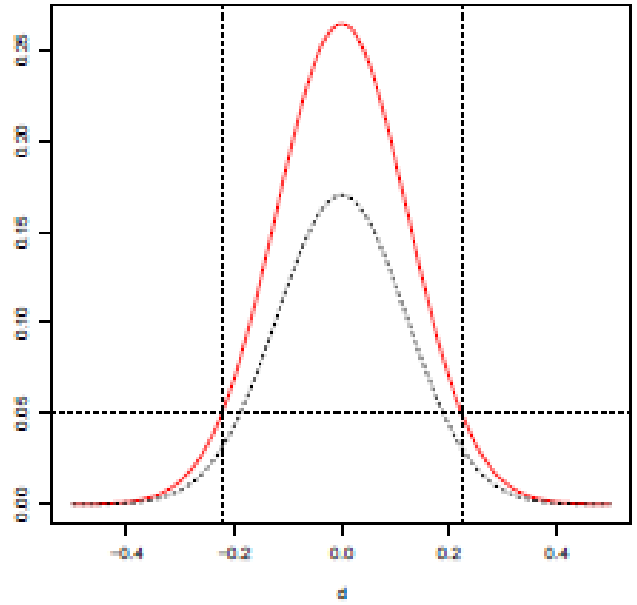
[1] Philips KF. J Pharmacokinet Biopharm (1990) [2] Tsai et al. Stat in Med (2014)

Power curve comparison of TOST & BOT

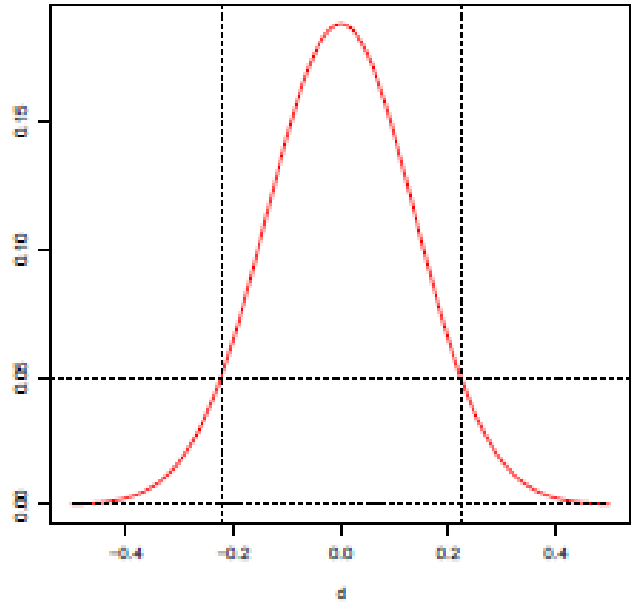
TOST (black dashed line) vs. BOT (red solid line)



$SE(\beta^{Tr}) = 0.07$
Type I error of TOST= 0.05



$SE(\beta^{Tr}) = 0.12$
Type I error of TOST= 0.03



$SE(\beta^{Tr}) = 0.14\ (\log(1.25)/1.645)$
Type I error of TOST= 0.00

RESEARCH ARTICLE

Efficient model-based Bioequivalence Testing

Kathrin Möllenhoff[1] | Florence Loingeville[2] | Julie Bertrand[3] | Thu Thuy Nguyen[3] | Satish Sharan[4] | Guoying Sun[5] | Stella Grosser[5] | Liang Zhao[4] | Lanyan Fang[4] | France Mentré[3] | Holger Dette[1]

Submitted to Statistics in Medicine September 2019

Parallel: type I error of TOST and BOT with asymptotic SE

Sampling time		Rich		Sparse	
Variability		Low	High	Low	High
NCA-TOST	AUC	0.052	**0.022**	-	-
	C_{max}	0.062	**0.012**	-	-
NCA-BOT	AUC	0.052	0.054	-	-
	C_{max}	0.062	0.052	-	-
MB-TOST	AUC	0.056	**0.004**	**0.076**	**0.006**
	C_{max}	0.058	**0.008**	0.066	**0.002**
MB-BOT	AUC	0.056	0.064	**0.076**	0.034
	C_{max}	0.070	0.060	0.070	0.058

Parallel: Power of TOST and BOT with asymptotic SE

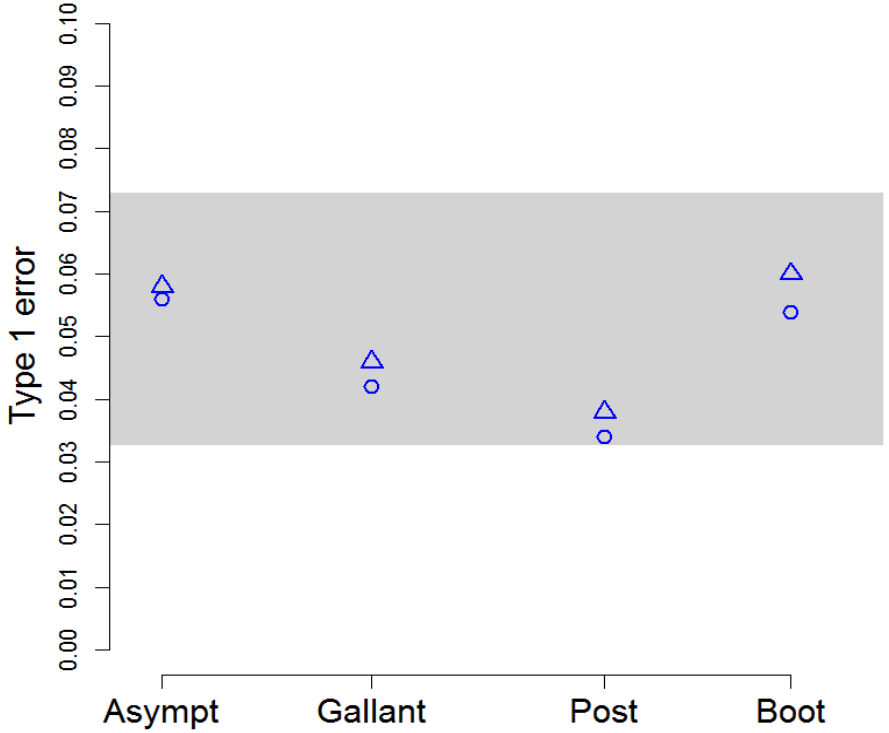
Sampling Time		Rich		Sparse	
Variability		Low	High	Low	High
NCA-TOST	AUC	0.998	0.132	-	-
	C_{max}	0.998	0.056	-	-
NCA-BOT	AUC	0.998	0.228	-	-
	C_{max}	0.998	0.154	-	-
MB-TOST	AUC	0.830	0.008	0.804	0.004
	C_{max}	1.000	0.024	1.000	0.016
MB-BOT	AUC	0.838	0.140	0.808	0.132
	C_{max}	1.000	0.138	1.000	0.116

Parallel: Type I error of TOST various SE

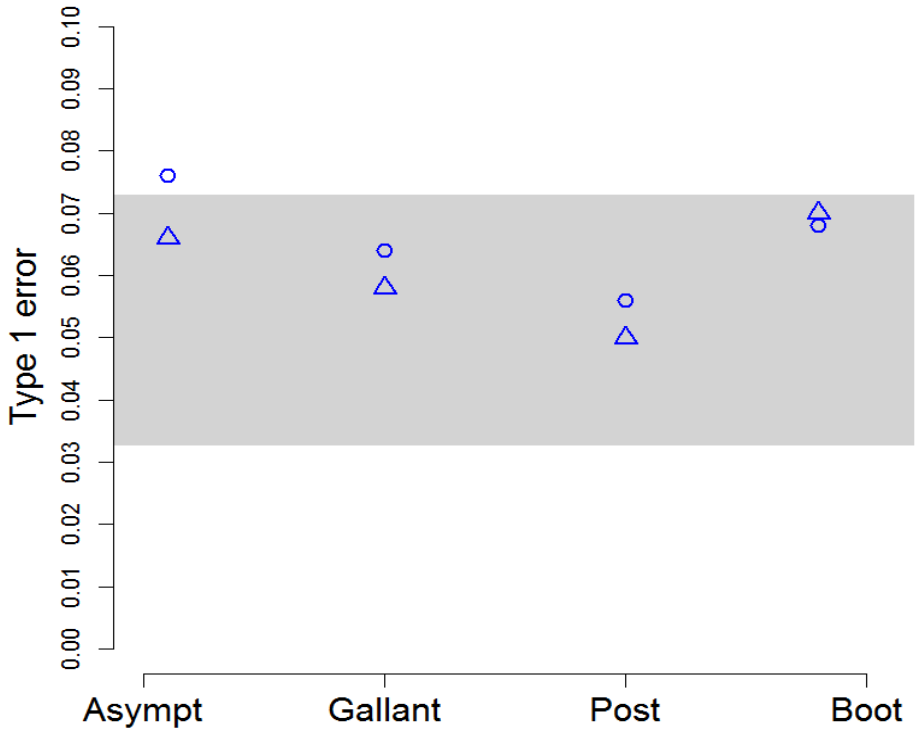
Low variability

Type I error of **MB TOST** on β_{AUC}^{Tr} (**o**) and β_{Cmax}^{Tr} (**Δ**)

N=40 n=10



N=40 n=3



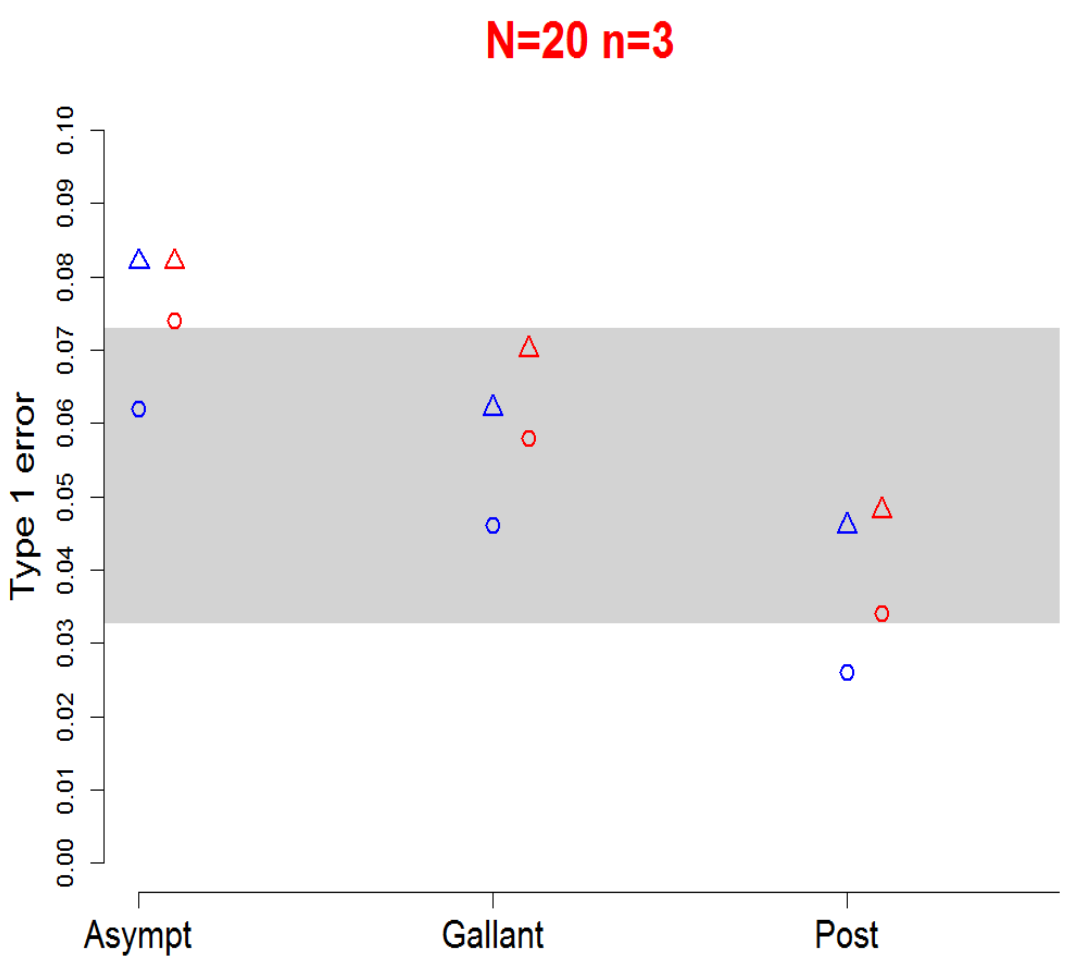
Computing time	0.25 min	0.25 min	5 min	43 min

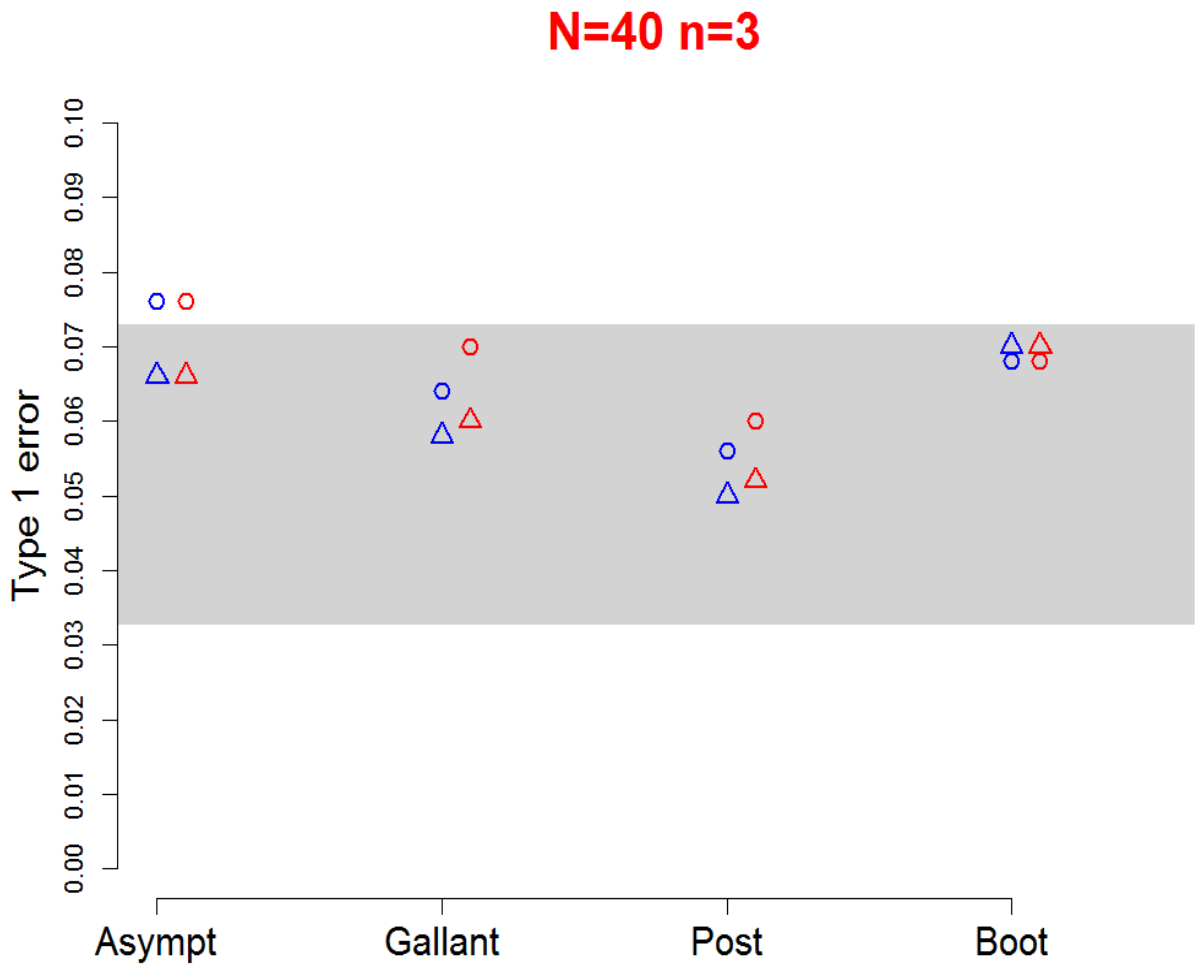
Power					
	β_{AUC}^{Tr}	0.830	0.782	0.772	0.832
	β_{Cmax}^{Tr}	1.000	1.000	0.966	1.000

β_{AUC}^{Tr}	0.804	0.762	0.712	0.800
β_{Cmax}^{Tr}	1.000	0.998	0.990	1.000

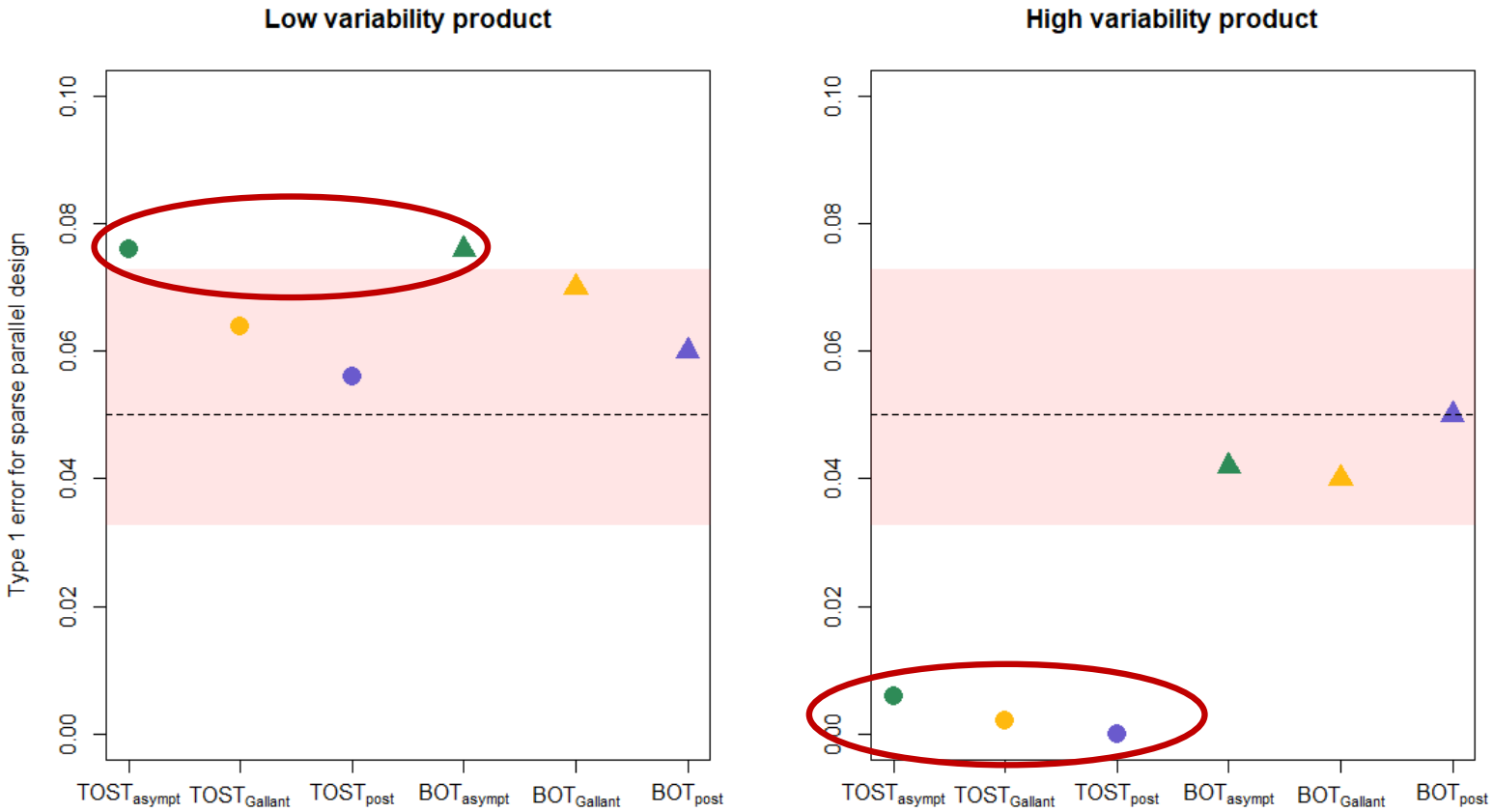
Parallel: Type I error of TOST various SE
Low variability

Type I error of **MB TOST** and **MB BOT** on β_{AUC}^{Tr} (**o**) and β_{Cmax}^{Tr} (**Δ**)





Parallel: main conclusion on type I error



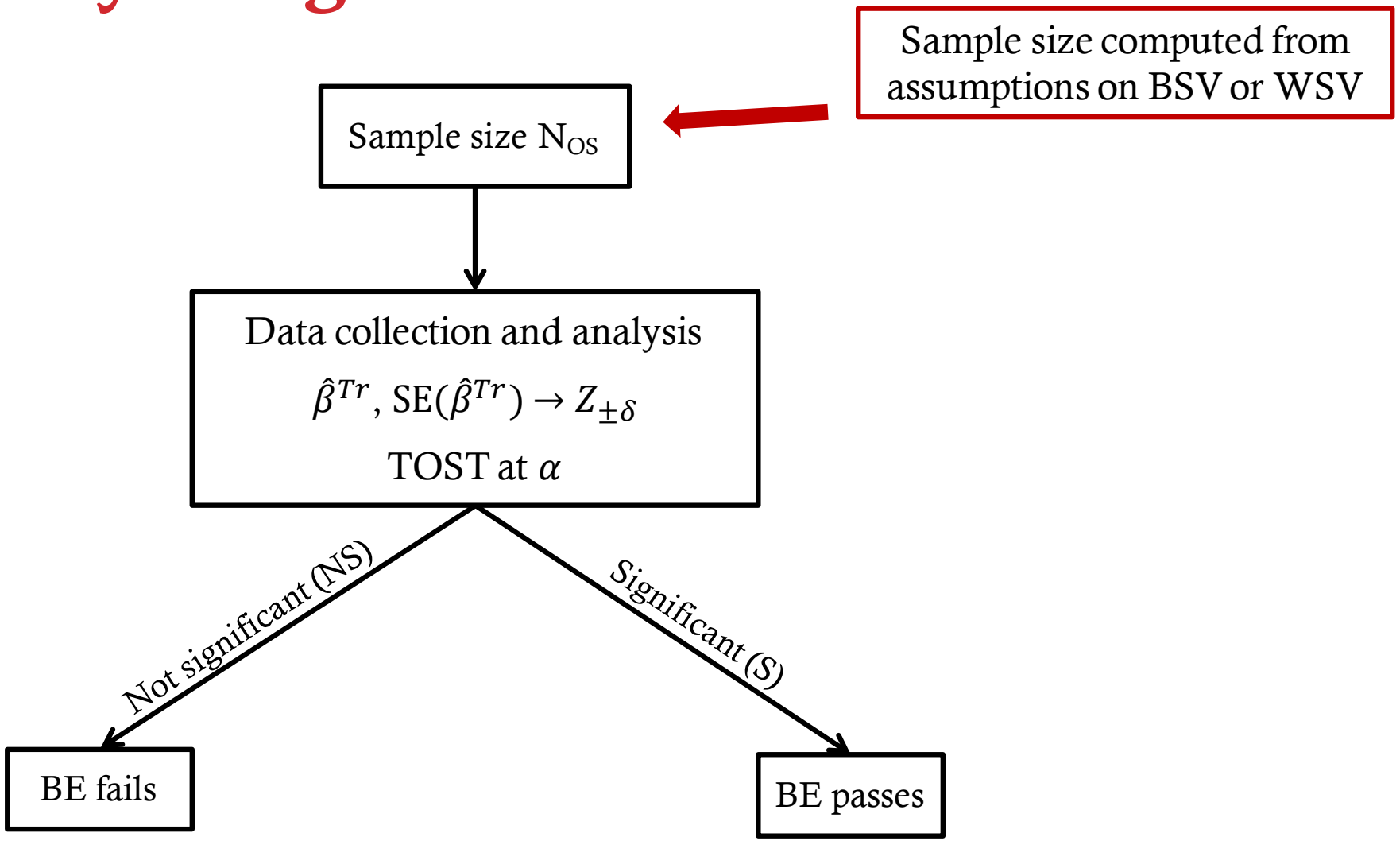
Objectives

1. To propose **new approaches** to correct for type I error inflation of TOST in MBBE and to evaluate them by **CTS**
   - Crossover designs
   - Parallel designs
2. To implement **two-stage sequential[1] and adaptive[2] designs** with model-based TOST and to evaluate them by **CTS**

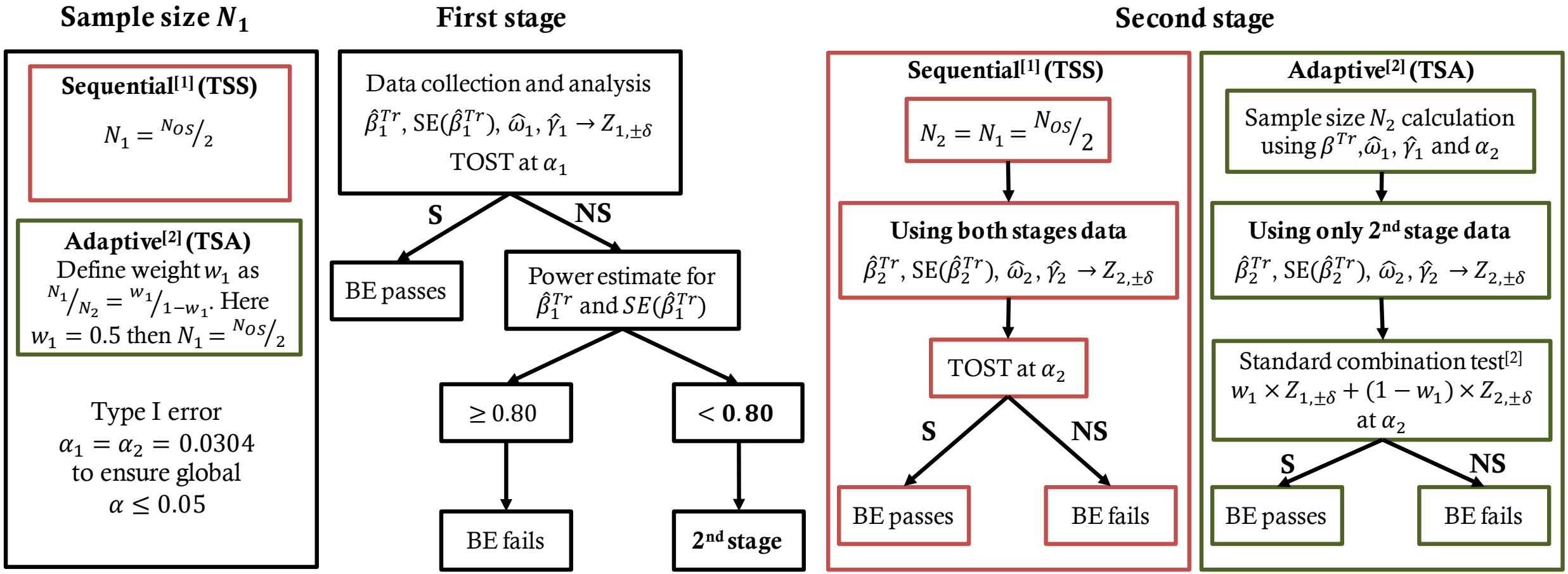
[1]: Kieser *et al.*, *Statistics in Medicine*, 2015

[2]: Maurer *et al.*, *Statistics in Medicine*, 2018

One-stage study design



Two-stage study designs: sequential or adaptive

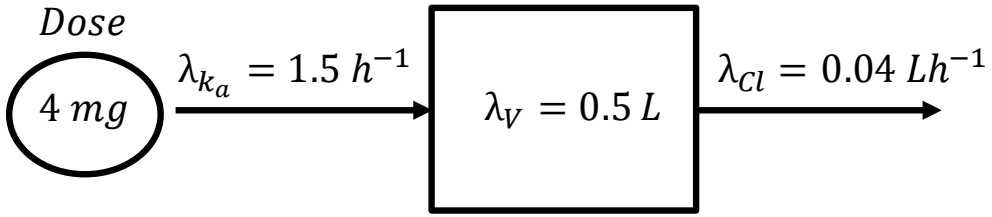


[1]: Kieser *et al., Statistics in Medicine*, 2015

[2]: Maurer *et al., Statistics in Medicine*, 2018

Simulation study

- PK model concentrations of theophylline[1]



- Rich S=study design
  - $n = 10$ sampling times $t = (0.25, 0.50, 1, 2, 3.50, 5, 7, 9, 12, 24\ h)$

    → Standard one-compartment PK model with rich sampling times
  - Parallel (low variability)

ω_{k_a} (%)	ω_V (%)	ω_{Cl} (%)	σ_{inter} (mg/L)	σ_{slope} (%)
22	11	22	0.1	10

  - Crossover

ω(%)	γ(%)	σ_{inter} (mg/L)	σ_{slope} (%)
50	15	0.1	10

Same ω and γ for all PK parameters $\beta^P = \beta^S = 0$

- Simulation under H_0: $\beta^{Tr} = \log(0.80)$ and H_1: $\beta^{Tr} = \log(1) = 0$
- 500 simulated data sets
- Evaluation of BE on $\boldsymbol{AUC}$ and C_{max} independently
- Estimation using SAEM algorithm in saemix (parallel) or Monolix (crossover)

Sample size calculation

- Assumptions
  - Type I error $\alpha = 0.05$; power $1 - \beta = 0.80$
  - Assumed $\beta^{Tr} = \log(0.95)$
  - Assumed correct values for fixed effects λ_l
  - **Three assumptions for variances:**

- Parallel

BSV ω (%)			**Residual errors standard deviations**	
Low	**True**	**High**	σ_{inter} (mg/L)	σ_{slope} (%)
10	22	30	0.1	10

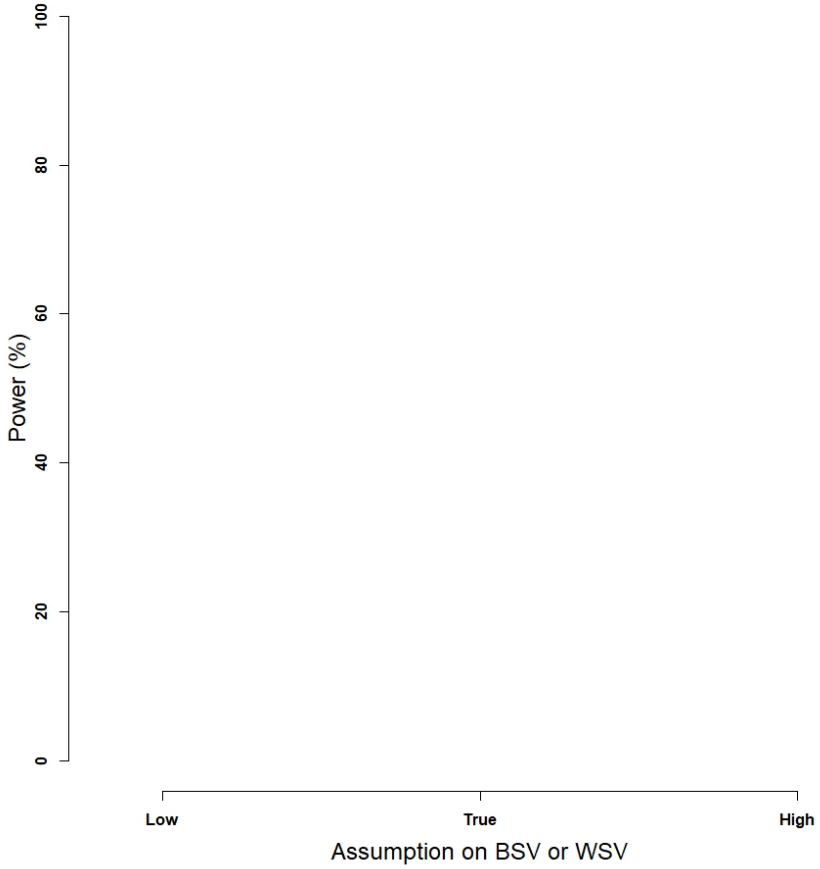
- Cross over

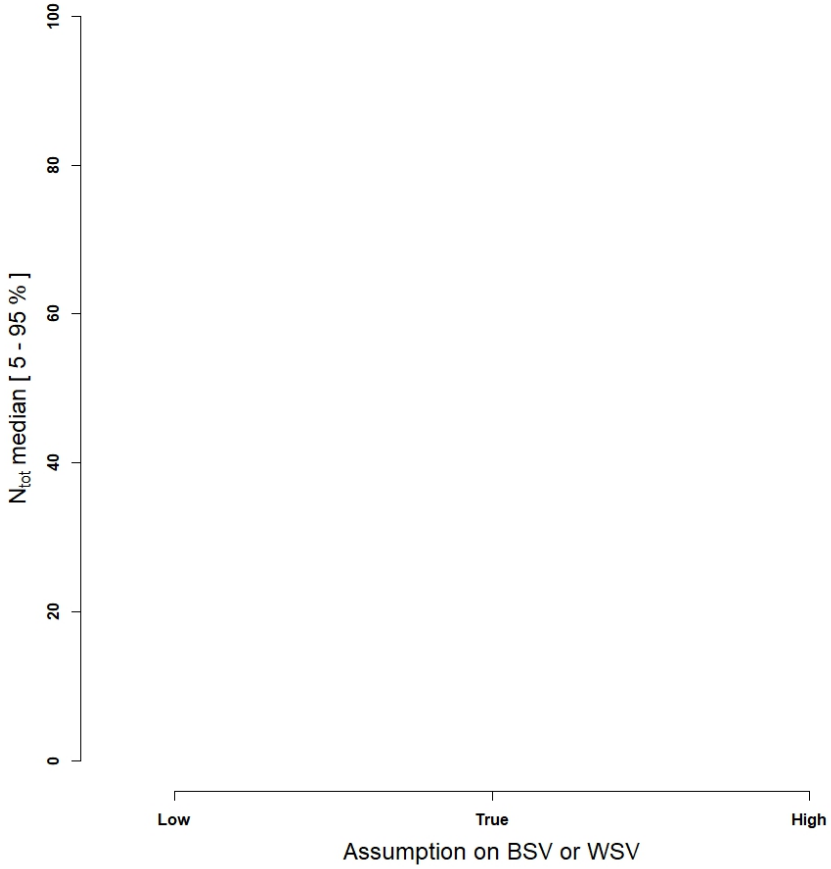
BSV ω (%)	**WSV γ (%)**			**Residual errors standard deviations**	
	Low	**True**	**High**	σ_{inter} (mg/L)	σ_{slope} (%)
50	5	15	25	0.1	10

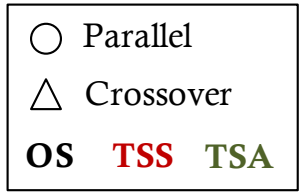
- Number of subjects for One Stage design computed using the expected population FIM (PFIM 4.0 software)[1]

[1]: Dumont *et al., Computer Methods and Programs in Biomedicine,* 2018

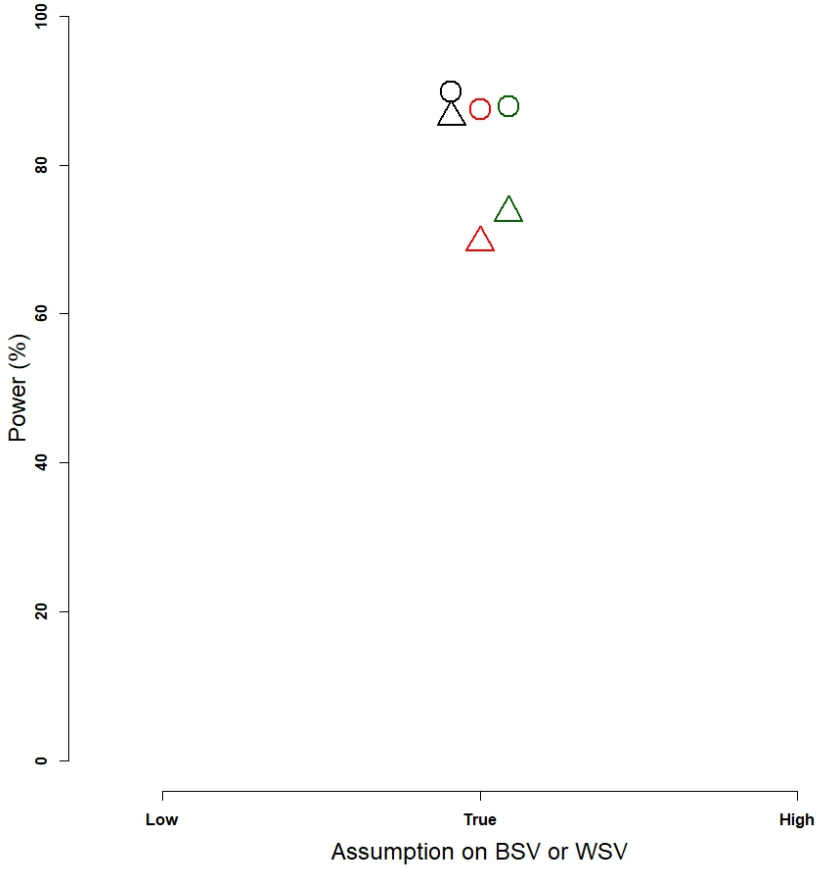
Under H_1 (Bioequivalence)

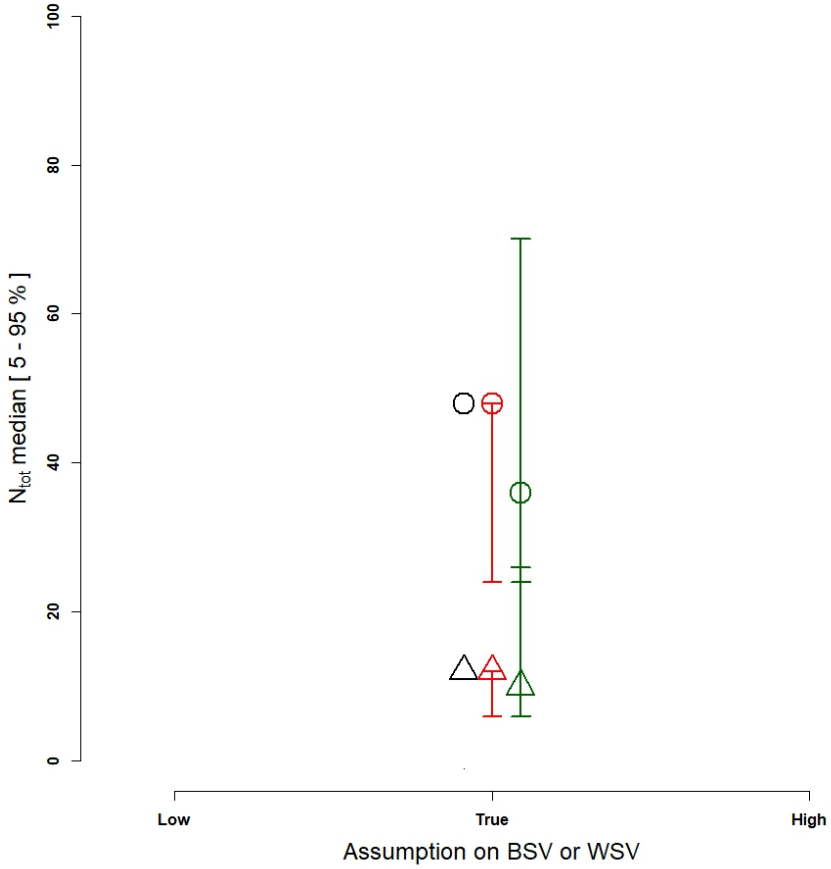


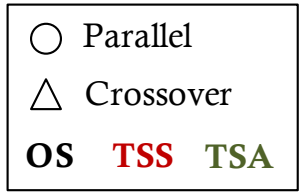




Under H_1 (Bioequivalence)







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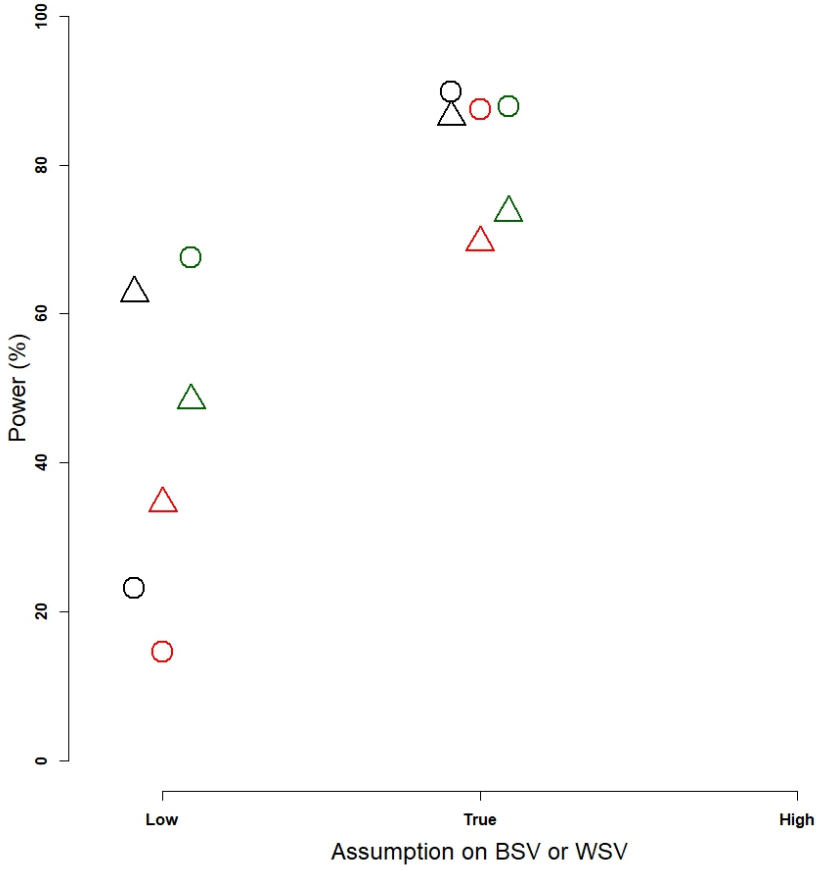

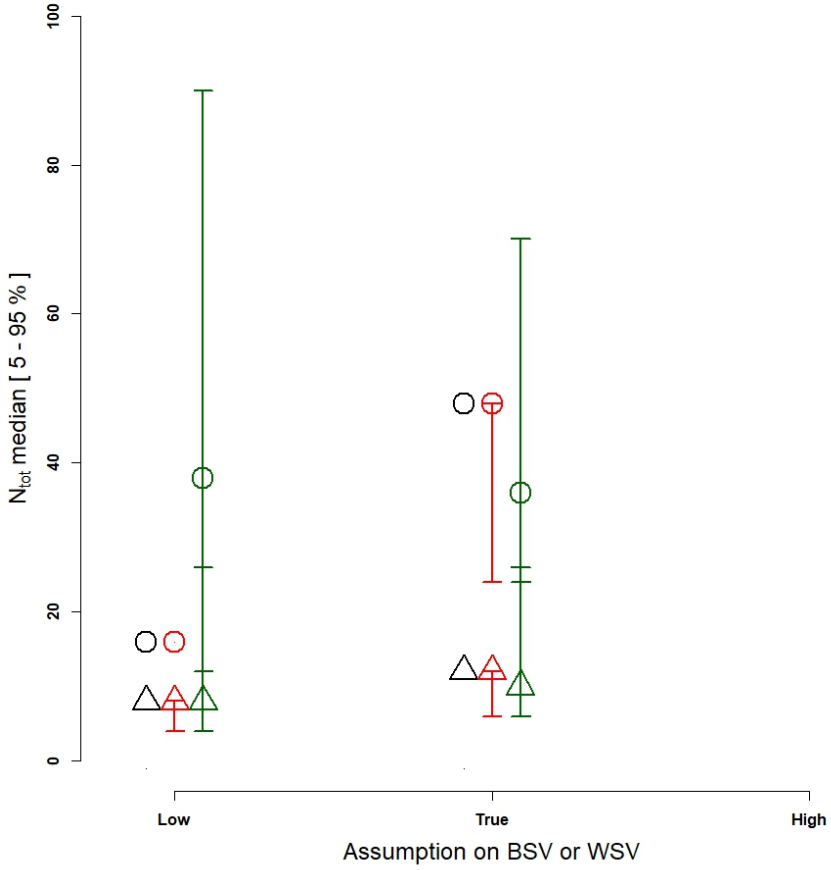

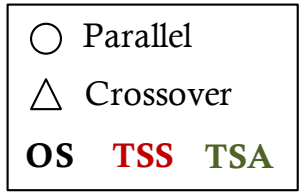

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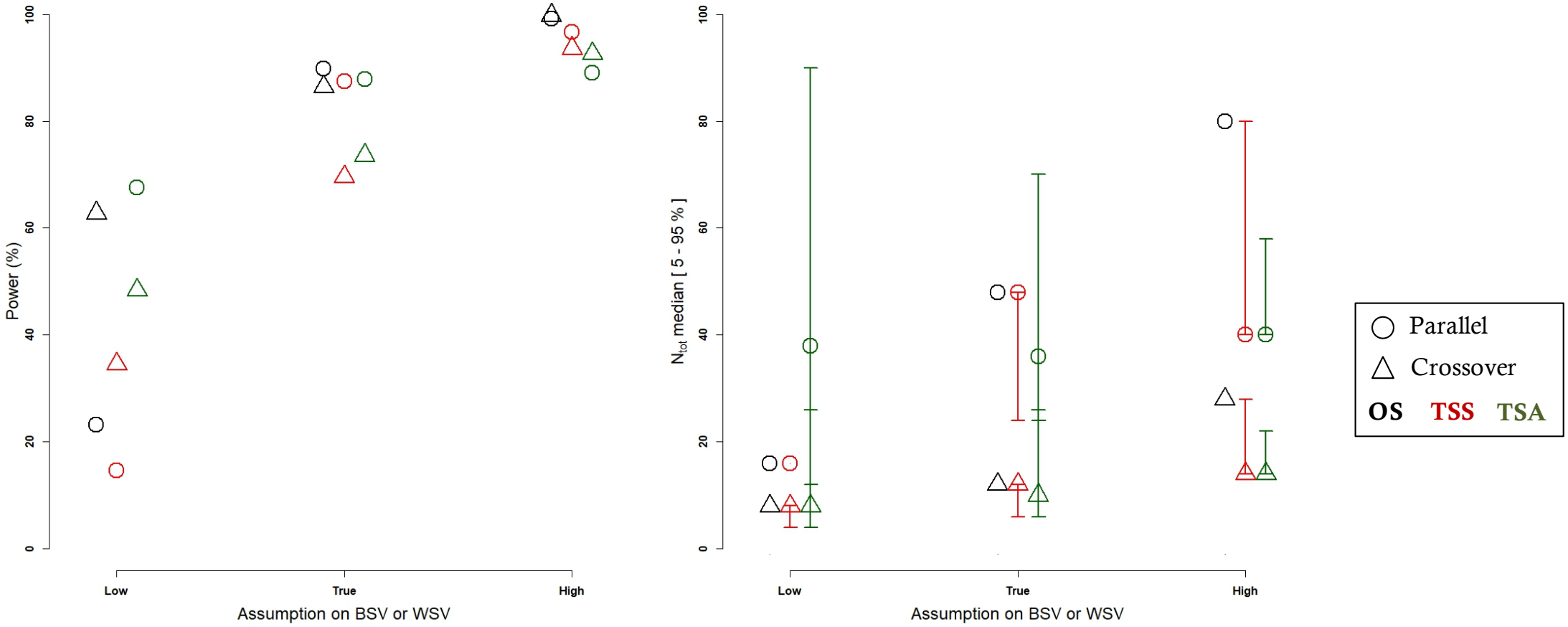
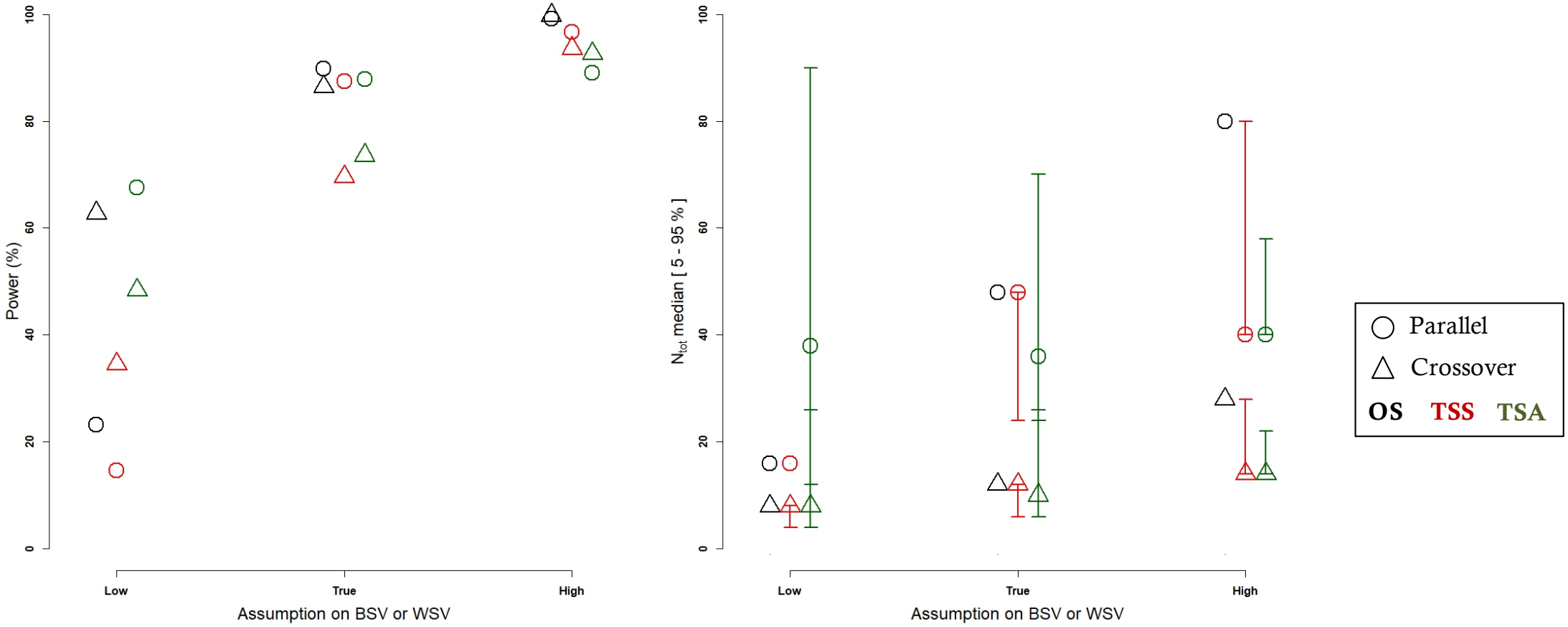


Under H_1 (Bioequivalence)



- **TSS** led to similar or lower N_{tot} than **OS**
- **TSS** power were lower than **OS**
- **TSA** led to higher N_{tot} when assumed variability low, lower N_{tot} when assumed variability high
- **TSA** power was higher than **OS** when assumed variability low, was slightly smaller than **OS** when assumed variability high

Conclusion

1. MBBE is feasible for parallel and cross-over designs
   - When variability is large compare to N, TOST could be problematic and BOT should be used
   - NLMEM-TOST based on asymptotic SE leads to an increased type I error, especially for sparse design
   - Three approaches were studied to get better SE: Bootstrap, posterior distribution and Gallant correction
     - Bootstrap too computationally intensive and not always enough correction
     - Full posterior distribution the best approach
       - Presently using Stan
       - Shoud be implemented in saemix/ Monolix (FDA Grant 2 year 2)
2. MBBE is feasible for two-stage designs (sequential or adaptive)
   - Preserved type I error in most cases (only rich design studied), pb of TOST for very small studies
   - **Two-stage sequential approach** of limited benefit when variability too low (loss of power), gain on number of individuals if variability too high
   - **Two-stage adaptive approach** can increase sample size if variability too low (increase of power), and reduce sample size when variability too low with only slight loss of power
   - Further extensions/evaluations of adaptive two-stage are needed for sparse design

Perspectives

- Perform analyses and simulations from real examples
  - FDA ophthalmic drug data set, Novartis, Roche, Servier data sets
  - Study influence of design, and of assumed model?
- Implement full posterior distribution in saem
- Extend two-stage designs with no asymptotic SE

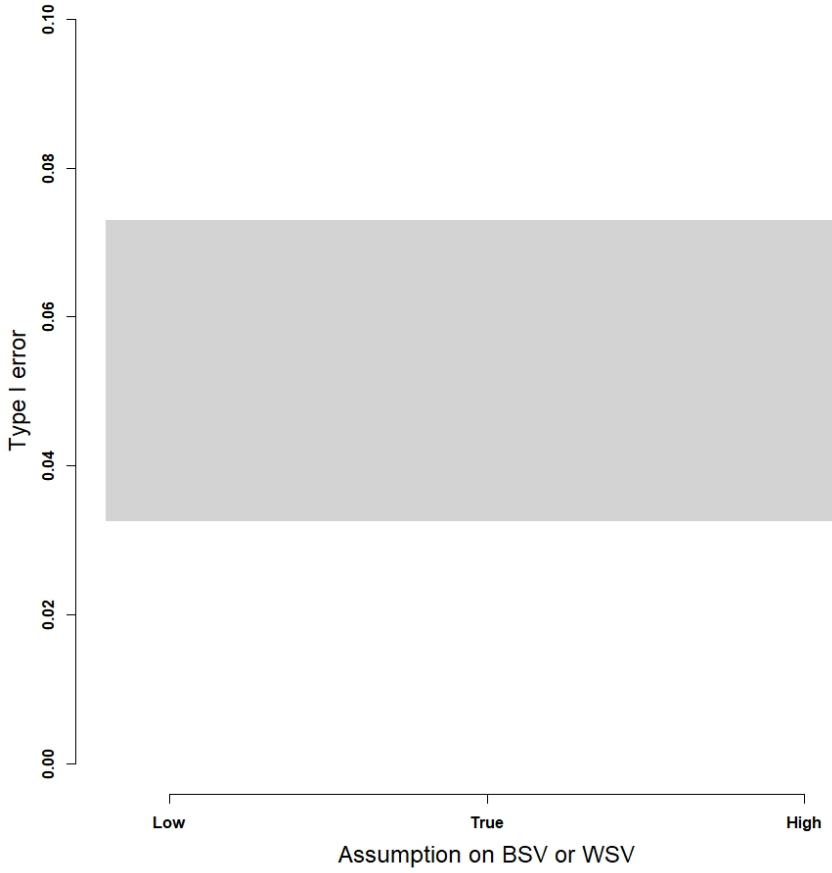
FDA Grant 2 (2 years)

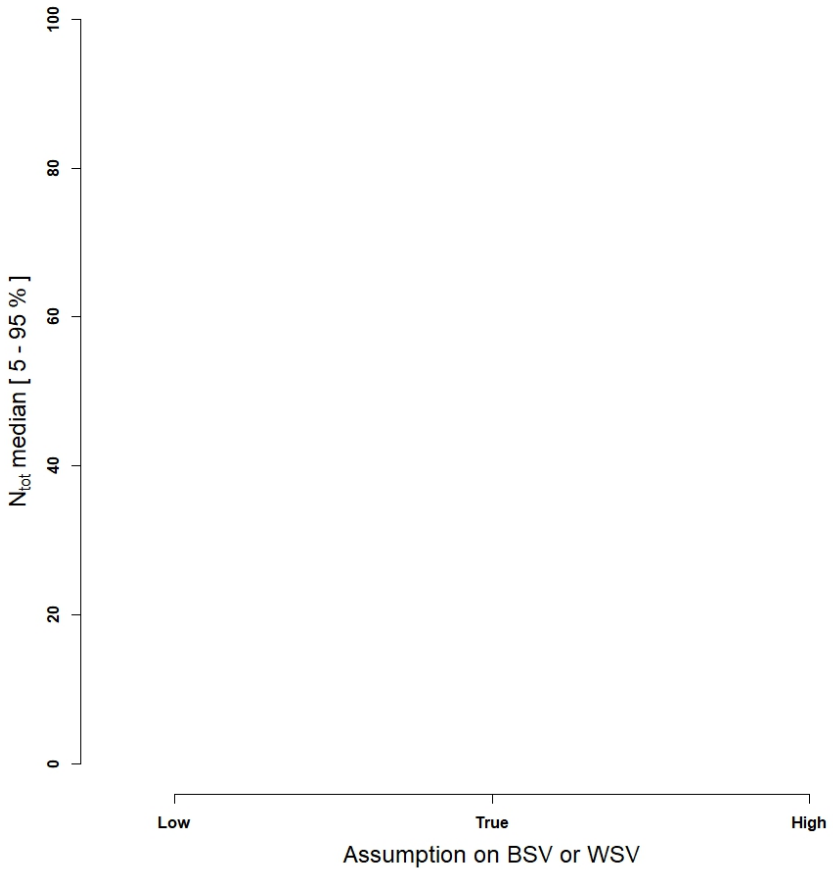
- INSERM: France Mentre, Julie Bertrand, *Florence Loingeville*, *Thu Thuy Nguyen*
- RUB: Holger Dette, *Kathrin Möllenhoff*
- Novartis: Frank Bretz, Didier Renard, Bjoern Bornkamp
- Roche: Francois Mercier
- Servier: Marylore Chenel

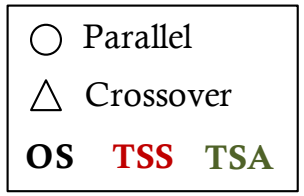
Backup slides

- Results of two-stage study designs under H_0

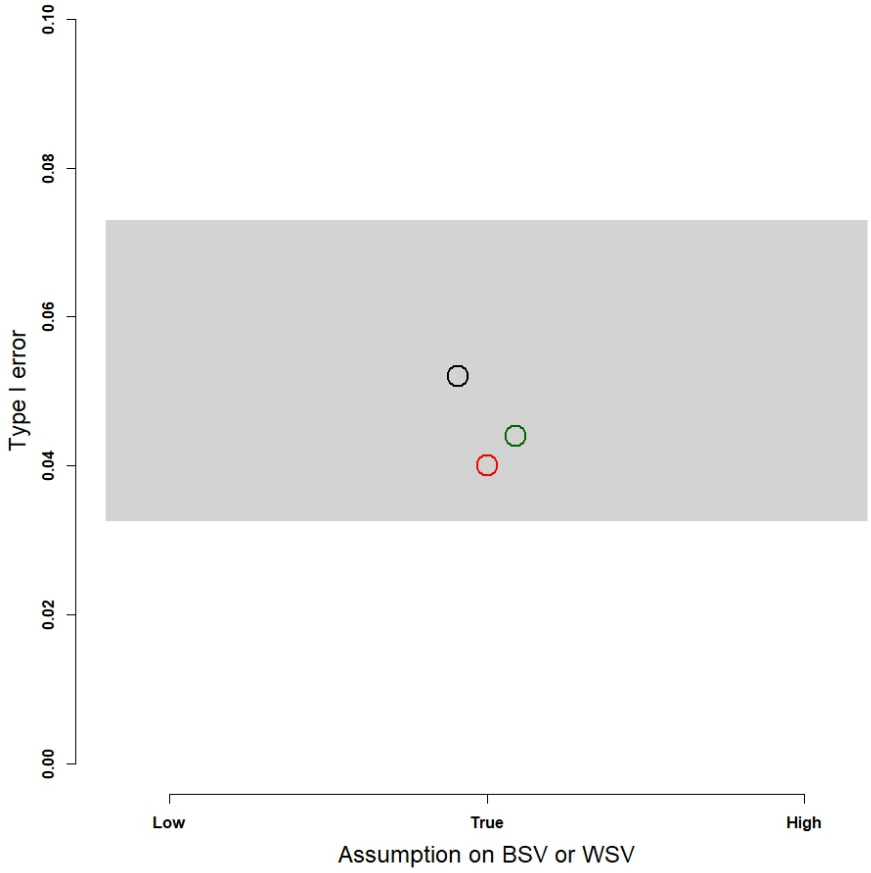
Under H_0 (No bioequivalence)

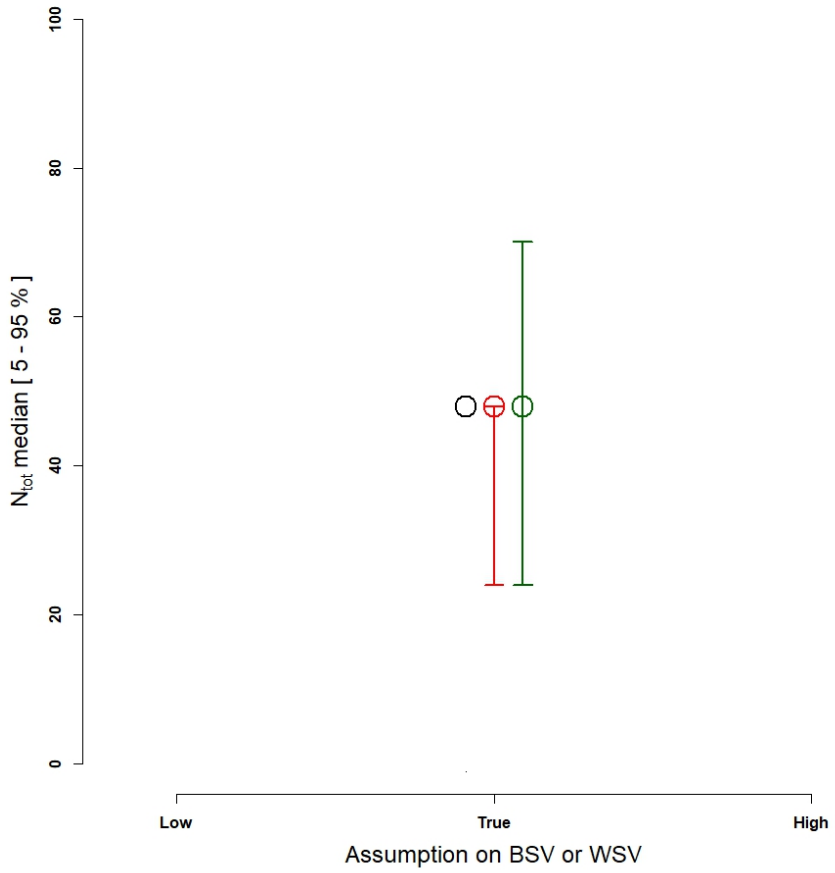


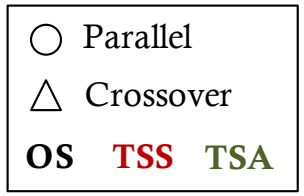




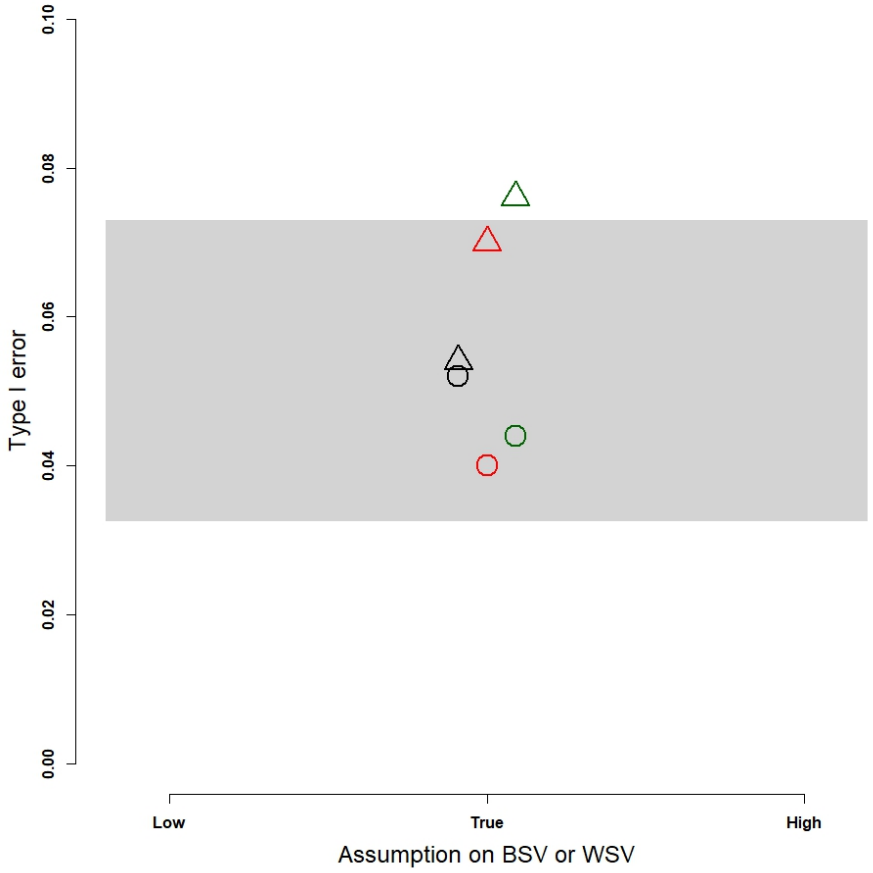
Under H_0 (No bioequivalence)

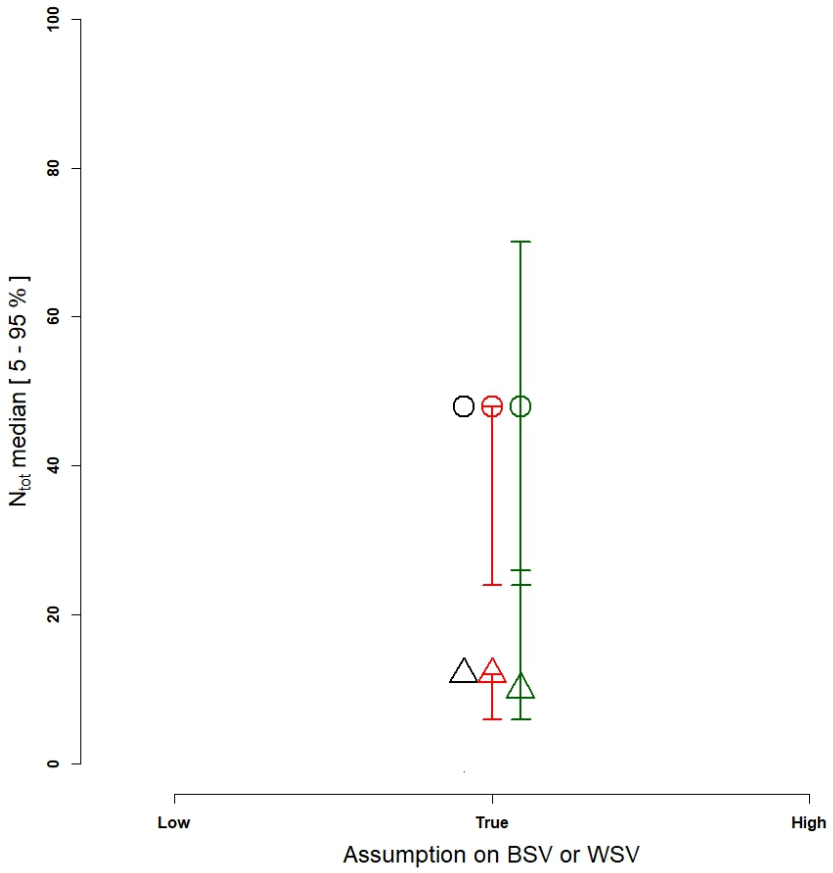


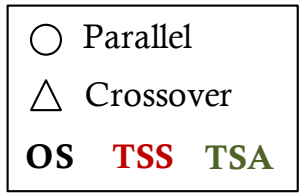




Under H_0 (No bioequivalence)







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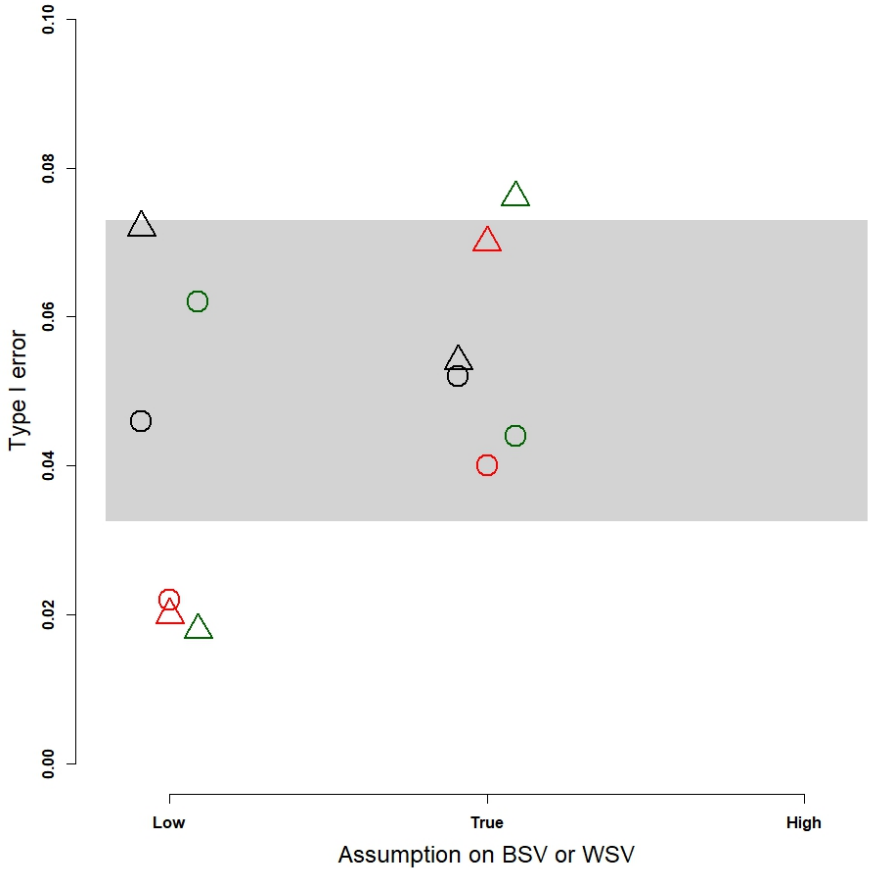
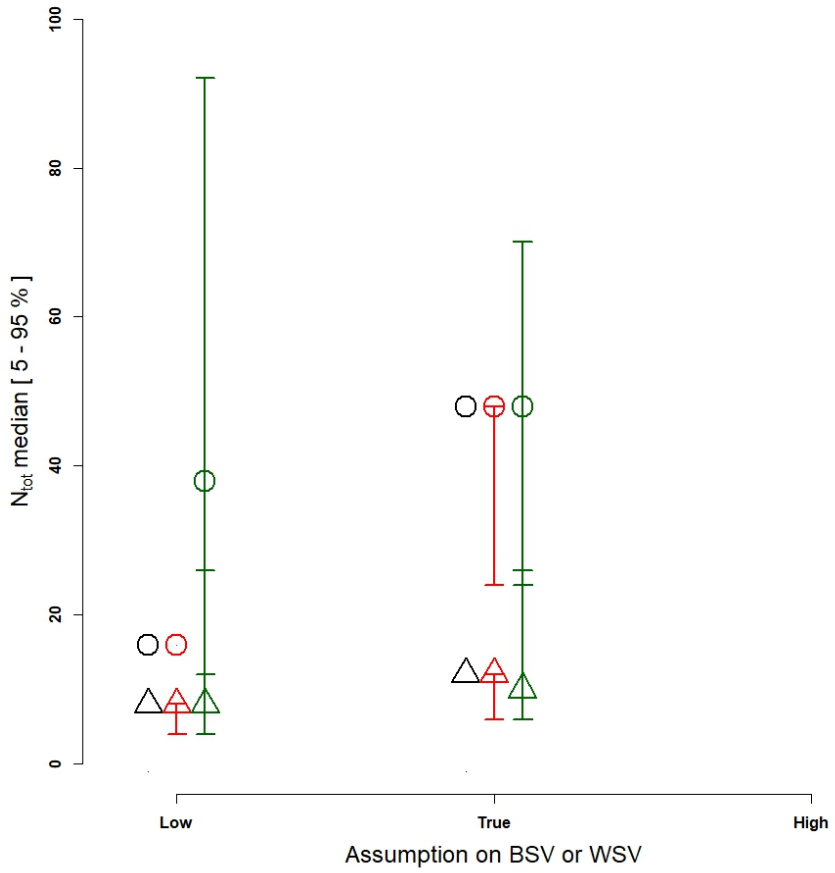
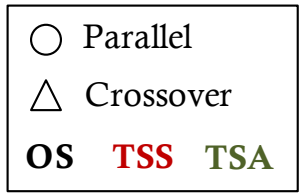
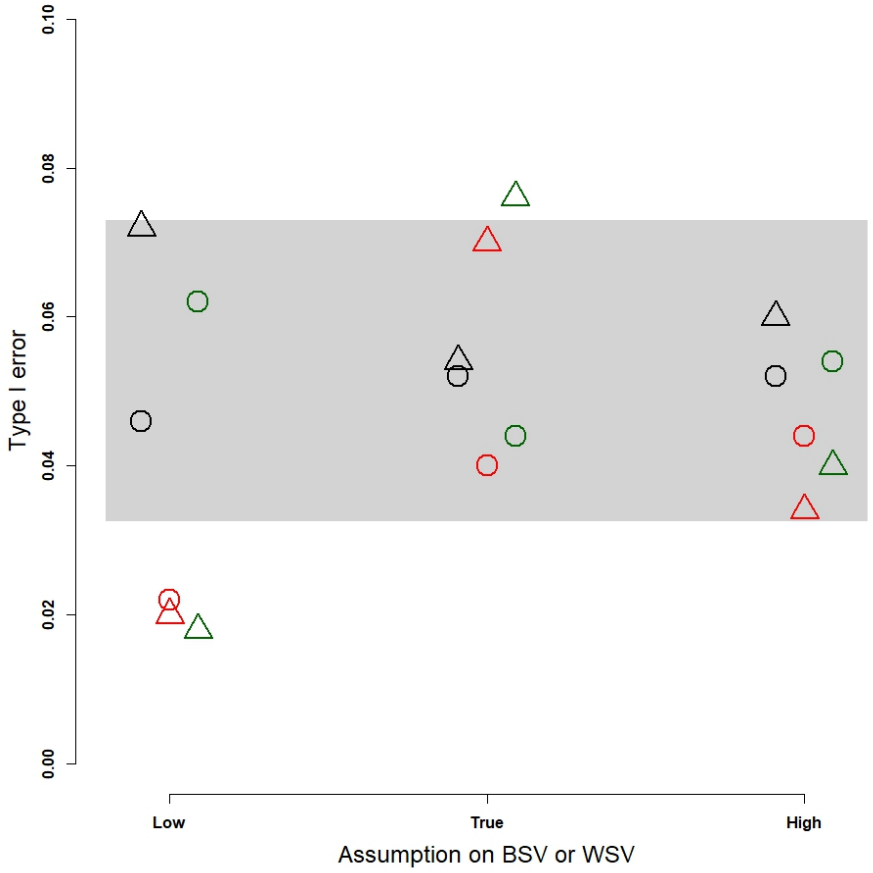
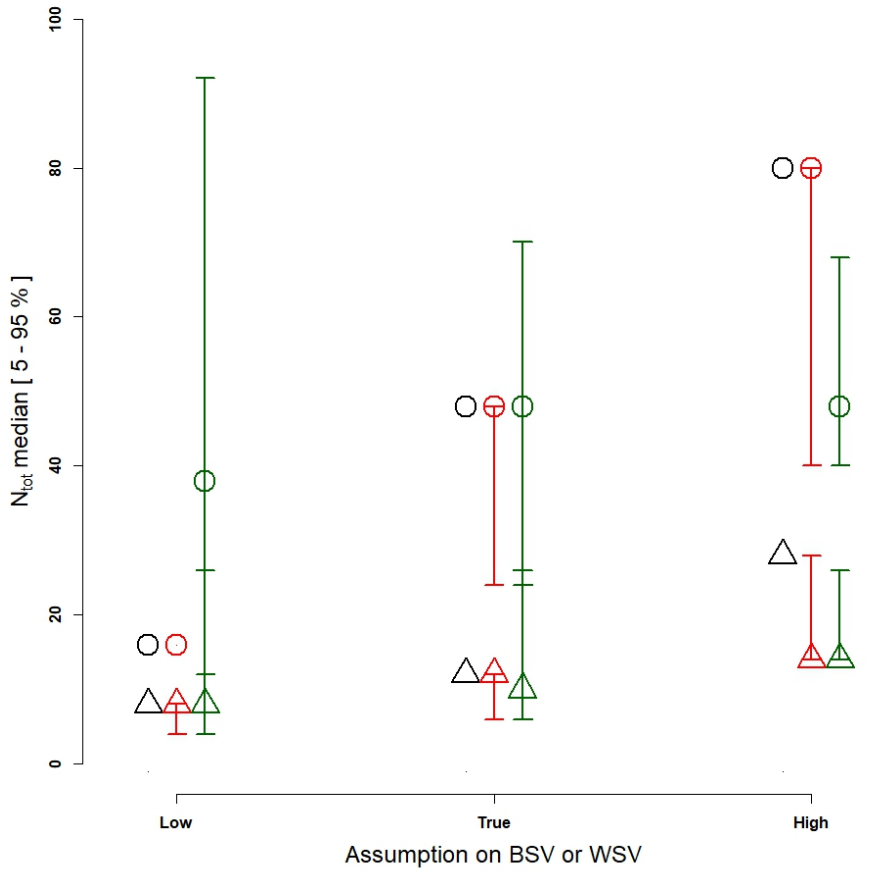


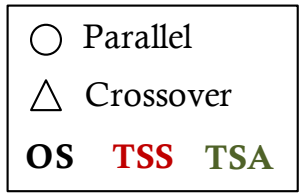




Under H_0 (No bioequivalence)







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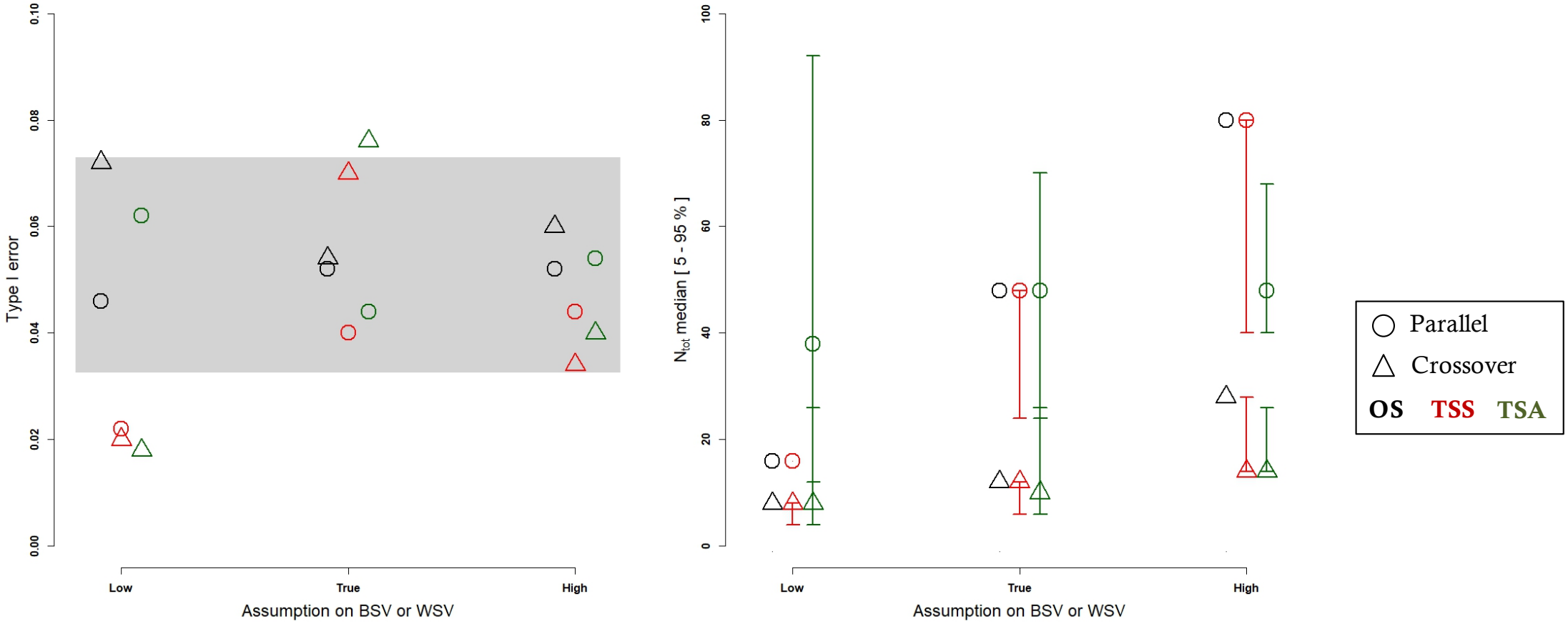

- **TSS** led to similar or lower N_{tot} than **OS**
- **TSA** led to higher N_{tot} when assumed variability low, lower N_{tot} when assumed variability high
- In most cases, **TSS** and **TSA** type I error estimates were within the $95\%PI = [0.0326 - 0.0729]$
  - Pb of TOST for low variability and low sample size in some TSS and TSA results