Influence of study design and associated shrinkage on power of the tests used for covariate detection in population pharmacokinetics

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Outline

1. **Context**
2. **Objectives**
3. **Materials and methods**
4. **Results**
5. **Conclusion & perspectives**

Context

Estimation of parameters

- Individual parameters
  - usually estimated in population analysis through a Bayesian methodology as Maximum *a posteriori*
- Used to
  - Predict individual responses
  - Select covariates
  - Draw model diagnostics plots…

Context
Shrinkage of random effects

- Occurs when few information is available for an individual (sparse design)
- Characterized by a shrunk *a posteriori* distribution of estimated random effects (η) towards the population mean
- In a previous article [1], the authors extended form linear mixed effects methodology [2] a formula to predict shrinkage of individual parameters estimation
- Through an extensive simulation study, this article showed a good prediction of observed shrinkage using the Bayesian information matrix (M_{BF}), avoiding extensive clinical trial simulation

1.Combes F *et al,* Pharm. Res, (in press 2013); 2. Fedorov V, presented at design of experiments (2011)

Context

Observed shrinkage

- Savic [1] explored the influence of sparse design on random effects distribution

$$Sh_k = 1 - \frac{Var(\hat{\eta}_k)}{\omega_k^2}$$

- They also studied the influence of shrinkage on the relationship between individual parameters and covariates
- In presence of high shrinkage (over 40%):
  - ✓ Change of distribution shape (non-normal) or in the mean value of $\hat{\eta}$
  - ✓ Correlation between random effects may be hidden or induced
  - ✓ **Covariate relationships may be hidden or induced**

→ To the author's knowledge, no exploration has been made regarding the impact of shrinkage on the power of tests used for covariate detection

1.Savic R, *et al,* AAPS J (2009)

Objective

Investigate the impact of various designs with various levels of associated shrinkages, on the power to detect the effect of a continuous covariate of:

1. The correlation test (CT) based on individual parameters
2. The likelihood Ratio Test (LRT)

Materials and methods

Notations

- Individual statistical model

$$y = f(\theta, \xi) + \varepsilon \qquad \text{with } \xi = \{t_1, \dots, t_n\}$$

$f(\theta, \xi)$ describing the PK model

- $\theta = \mu e^{\eta}$
  - Fixed effects

    $\mu = (\mu_1, \dots, \mu_k, \dots, \mu_p)$
  - Random effects

    $\eta \sim \mathcal{N}(0, \Omega)$
  - Variance-covariance matrix of random effects

    $\Omega = diag(\omega_1^2, \dots, \omega_p^2)$

- Residual error

  $\varepsilon \sim \mathcal{N}(0, \Sigma(\theta, \xi))$
  - Matrix of variance of residual error

Materials and methods

Prediction of shrinkage

$$I - W(\xi) = M_{BF}(\xi)^{-1}\Omega^{-1}$$

- M_{BF} approximated by first order linearization of the model proposed by Merlé *et al* [1]

$$M_{BF}(\xi) = \mathrm{M}^T F(\mu, \xi)^T \Sigma(\mu, \xi)^{-1} F(\mu, \xi)\mathrm{M} + \Omega^{-1}$$

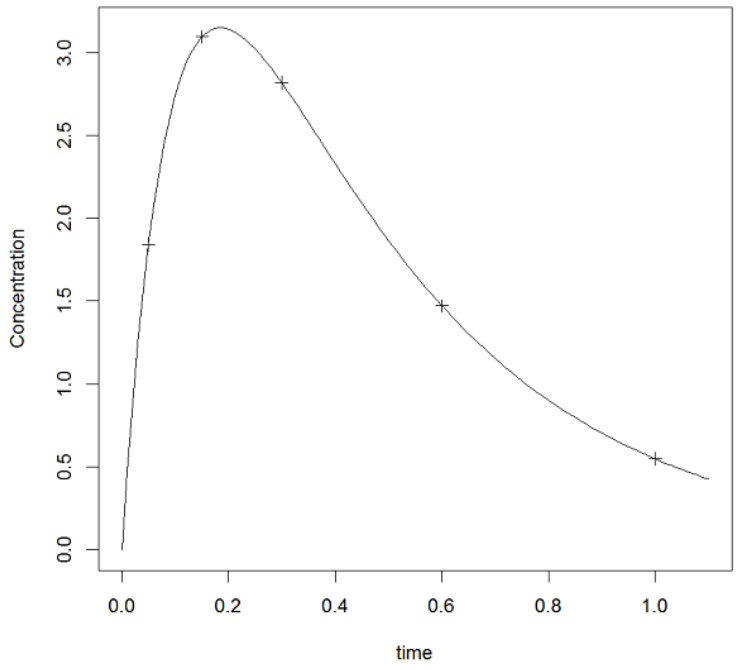
Where $\mathrm{M} = \mathrm{diag}(\mu_1, \ldots, \mu_p)$ and $\mathrm{F}(\mu, \xi) = \frac{\delta f(\theta, \xi)}{\delta \theta}$

1. Merlé Y *et al,* J Pharmacokinet Biopharm (1995)

Materials and methods

Pharmacokinetic example

- Inspired from Combes *et al* [1]
- Simple PK model with one compartment, oral absorption and a linear elimination was simulated



- Two considered scenarios

Table 1: Simulation values

Parameter	**Scenario 1**	**Scenario 2**
k_a	10	
V	0.2	
CL	0.5	
ω (%)	50	20
σ_{slope} (%)	30	40
σ_{inter}	0.15	

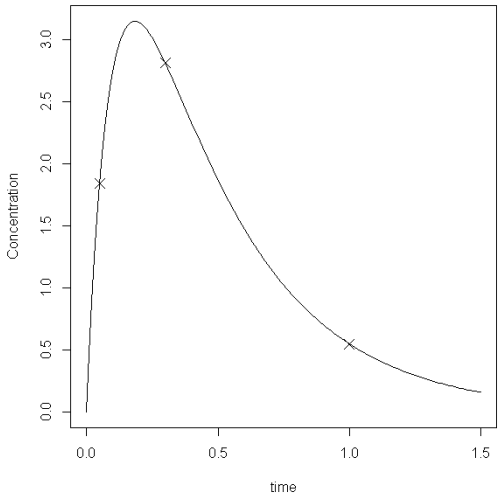
1.Combes F *et al.* Pharm Res (Epub 2013)

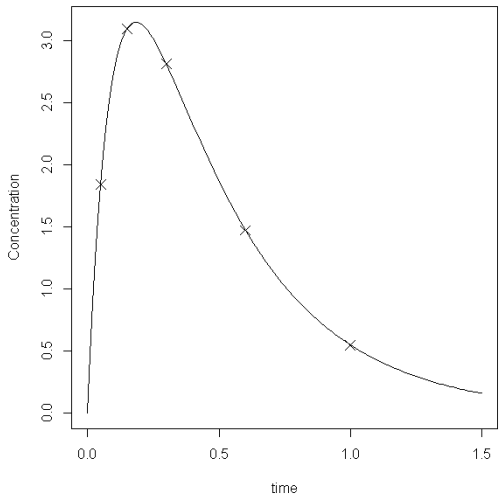
Materials and methods

Study designs

- 500 subjects were simulated with 2 (D2), 3 (D3) or 5 (D5) samples per subject
- **D2**
  - 3 groups of patients with 1/3 each
  - 3 elementary designs:

    {0.05; 0.3}, {0.05; 1}, {0.3; 1}
- **D3**
  - {0.05; 0.3; 1}
  - One group of patients
- **D5**
  - {0.05; 0.15; 0.3; 0.6; 1}
  - One group of patients





1.Combes F *et al.* Pharm Res (in press 2013)

Materials and methods

Covariate

- Covariate model
  - Weight (WT) following a log normal distribution with median = 70kg and 10% CV
  - Covariate model modeled as a power function

$$\theta_i = \mu \left(\frac{WT_i}{med(WT)} \right)^{\beta} e^{\eta_i}$$

- Detection of Covariate effect
  - Pearson correlation test (CT)
    - Standard correlation test between two continuous variables
    - Pearson test between η and WT
  - Likelihood ratio test (LRT)
    - Test of log-likelihood difference between two nested models
    - With or without covariate effect

Materials and methods

Simulation and estimation

- **Simulation** of 1000 datasets for each design, scenario with a WT effect on V with **three levels of covariate effect**
  - No effect : $\beta = 0$
  - Middle ($\beta = 0.2, 0.5$) or strong effect ($\beta = 0.5, 1$)
- **Evaluation of algorithm performance**
  - Simulation for $\beta = 0$, without any covariate
  - Estimation by NONMEM 7.2 with FOCEI or SAEM (SAEM with IMP for likelihood computation following the "expert" options in [1]), with β fixed to 0
  - Computation of the relative error (RE%) for each population parameter estimate
- **Evaluation of test of covariate effect**
  - CT: Estimation of the model without covariate effect
  - LRT: Estimation of the model with and without covariate effect
  - For both tests, computation of the percentage of significative tests

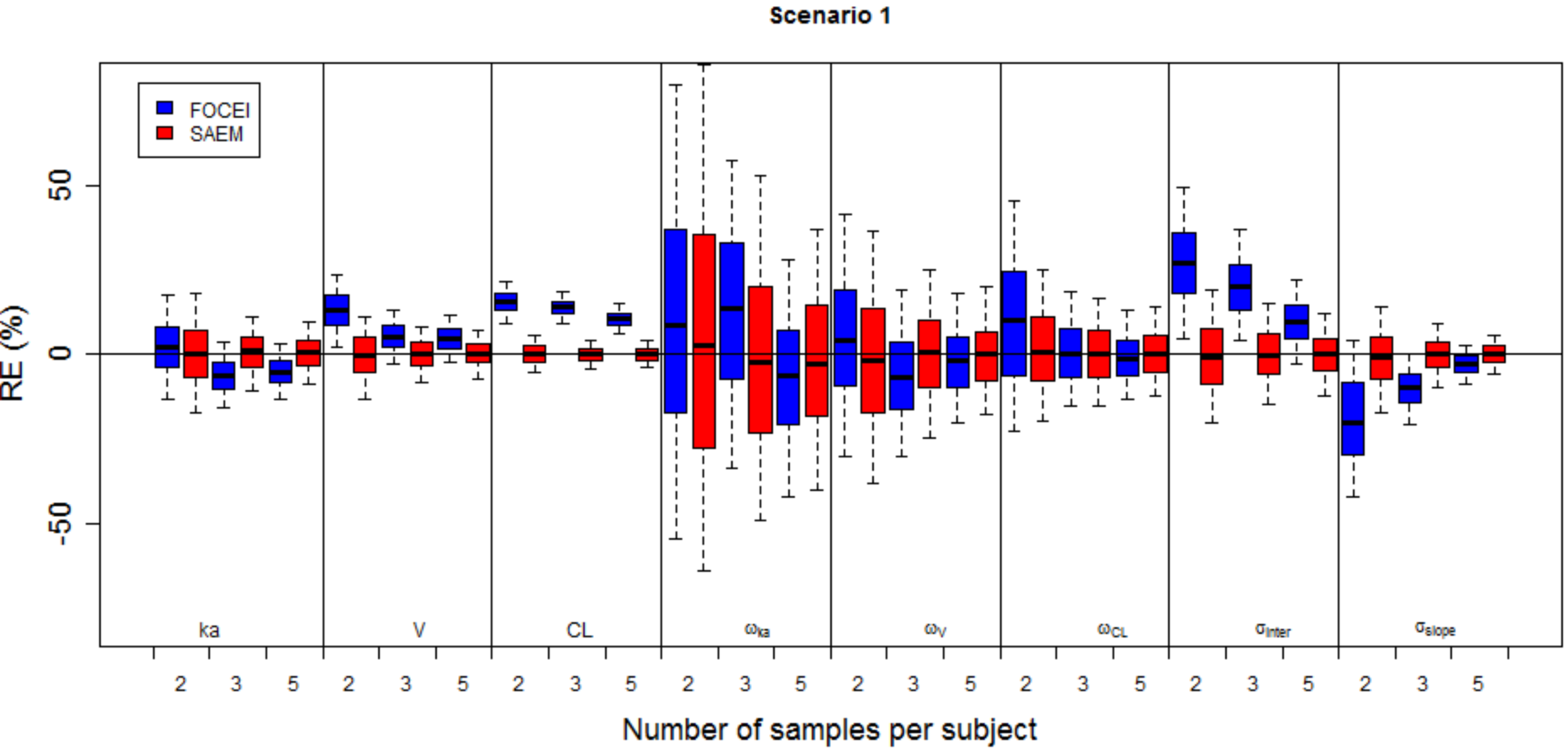
1.Gibianski L, *et al*, J pharmacokinet pharmacodyn (2012)

Results

1. *Algorithm performance*
2. *Influence of design on test of covariates*

Results

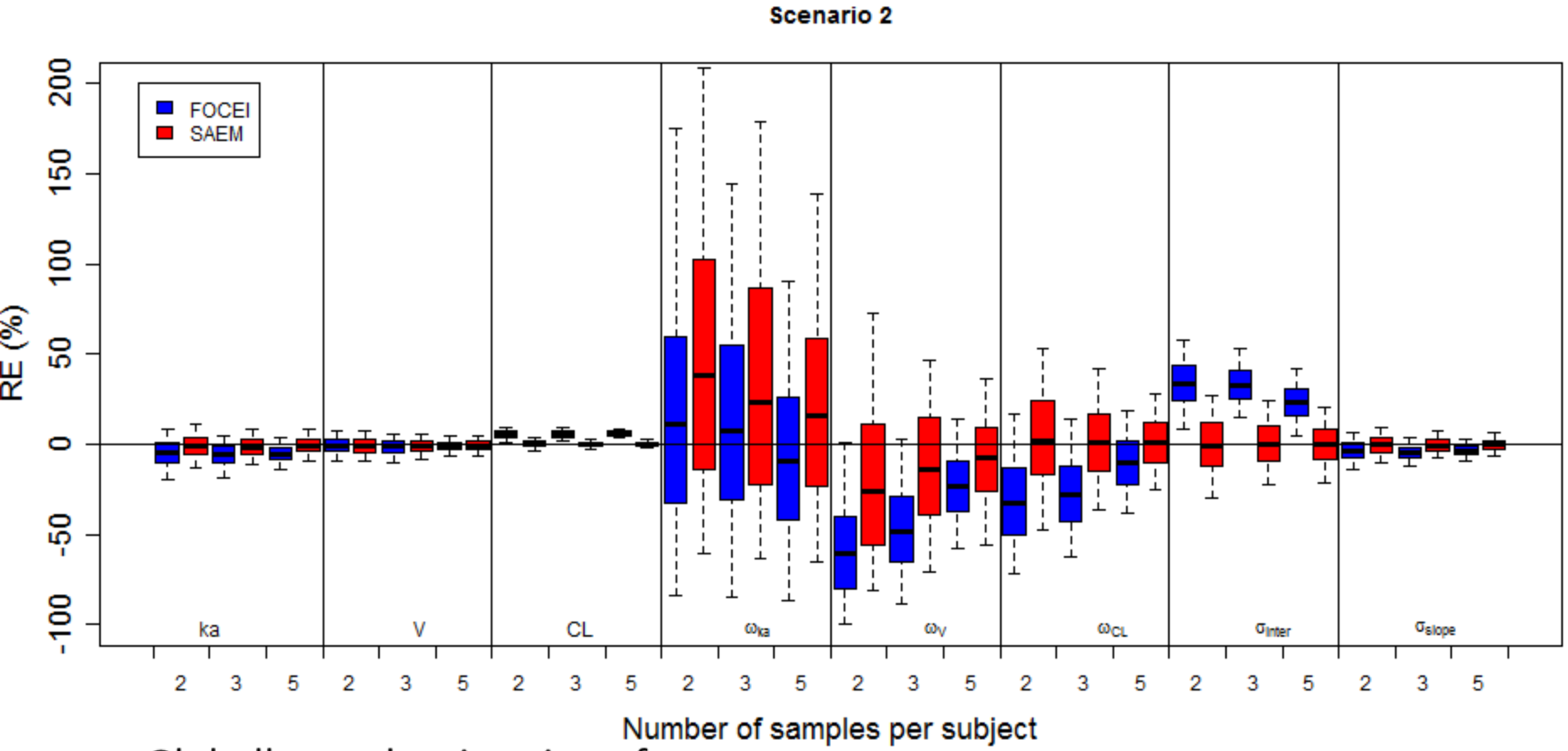
Scenario 1



- Globally good estimation of parameters
- Estimation of the variances of random effects less precise for the 2 samples design
- SAEM less biased than FOCE in all cases

Results

Scenario 2



- Globally good estimation of parameters
- Estimation of the variances of random effects less precise than scenario 1

Results

1. *Algorithm performance*
2. *Influence of design on test of covariates*

Following results presented for SAEM

Results

Predicted shrinkage

Table 2: Predicted shrinkage values (%)

(* : mean value on the 3 design)

	Scenario 1		Scenario 2	
Parameter	**V**	**CL**	**V**	**CL**
*D2**	56	43	84	85
D3	38	22	78	69
D5	31	14	72	59

Scenarios 1 and 2 allow to simulate a wide range of predicted shrinkage

Results

Type one error and power

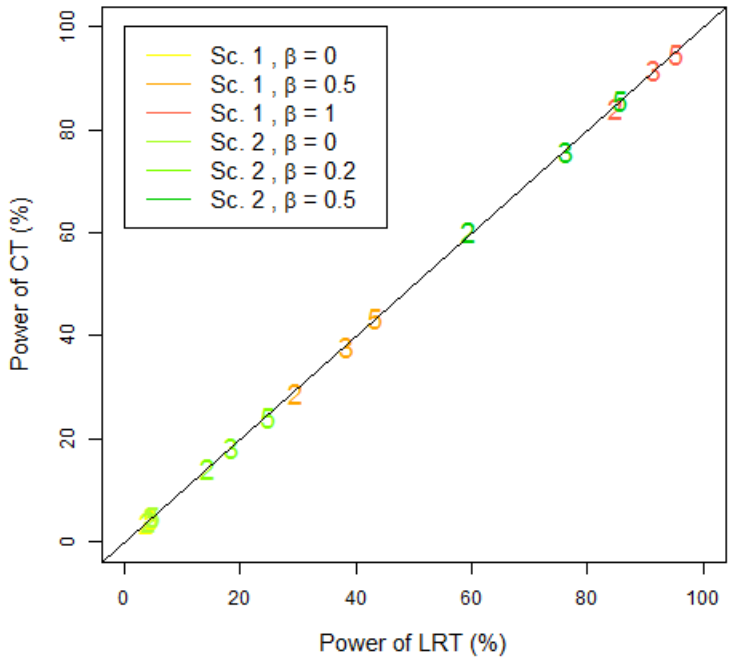
Table 3: Type one error and power of test (%) (SAEM)

Design	**Test**	**Scenario 1**			**Scenario 2**		
β		*0*	***0.5***	***1***	*0*	***0.2***	***0.5***
D2	LRT	3.8	29.7	84.8	4.2	14.3	59.4
	CT	3.9	29.1	84.3	4.0	14.4	60.5
D3	LRT	4.6	38.3	91.6	4.6	18.6	76.2
	CT	4.3	37.9	91.6	4.9	18.3	76.0
D5	LRT	4.8	43.5	95.4	5.0	25.0	85.7
	CT	4.7	43.6	94.9	5.0	24.2	85.8

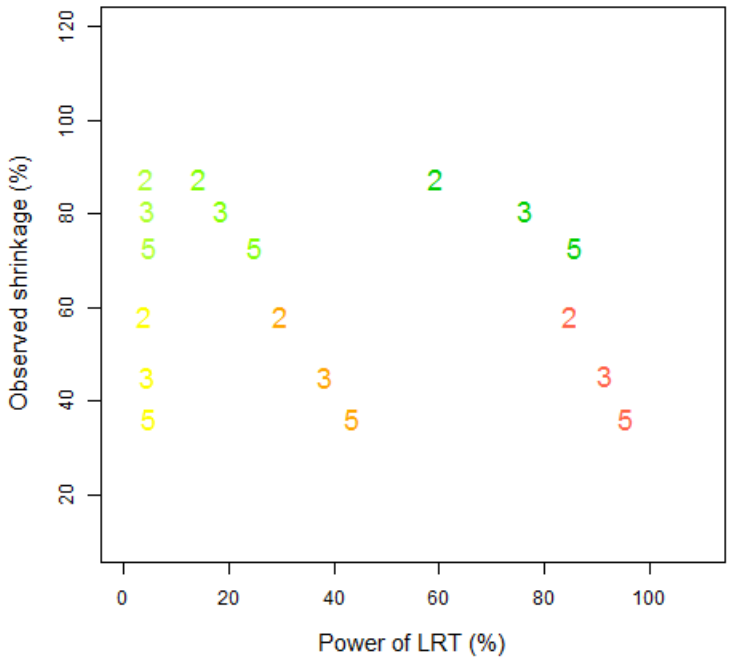
- Type one error
  - Values close to 5%
- Power
  - As expected, power directly linked with the level of covariate effect
  - For a given β, power decrease with the informativeness of the design

Results

LRT vs CT



LRT vs observed shrinkage



- As already noticed, influence of design, and therefore of shrinkage, on power of test is moderate compared to the influence of the effect size
- Whatever the design and the extend of the covariate influence, same power and type one error between LRT and CT
- LRT needs twice as much (H_0 and H_1) simulation-estimation processes than CT

Conclusion

- Importance of an accurate selection of NONMEM 7.2 algorithm and options, FOCEI being less accurate and less precise than SAEM, even for rich designs

- Moderate influence of design (number of samples) and its associated shrinkage on the power of tests to detect covariate effect. However, great influence of the level of covariate effect (β) on power

- No higher power for LRT than a simple correlation test for individual estimates, even with high shrinkage. Performing CT to detect covariate effect should be privileged as this test is less time and resource-consuming

Perspectives

- Confirmation of results in more challenging conditions
  - Fewer number of subjects
  - More complex pharmacokinetic model (*eg*: TMDD model [1])

- Influence of design on covariate selection
  - Between several covariate effect simulated on the same PK parameter
  - LRT and CT

1.Frey N, *et al*, J Clin pharmacol (2010)

Thanks for your attention

Q&A

Comments and remarks

Back-up slides

Context
Design evaluation and optimization in NLMEM

- Savic [1] explored the influence of sparse design on random effects distribution

- They also studied the influence of shrinkage on the relationship between individual parameters and covariates
- In presence of high shrinkage (over 40%):
  - ✓ Change of distribution shape (non-normal) or in the mean value of $\hat{\eta}$
  - ✓ Correlation between random effects may be hidden or induced
  - ✓ **Covariate relationships may be hidden or induced**

→ To the author's knowledge, no exploration has been made regarding the impact of shrinkage on the power of tests used for covariate detection

Mentré *et al* Biometrika,1997. Retout *et al* Stat Med, 2002. Bazzoli *et al* Stat Med, 2009. Merlé *et al*, J Pharmacokinet Biopharm. 1995

Materials and methods

Design evaluation for individual estimates

- Bayesian Fisher information matrix (M_{BF})

$$M_{BF}(\xi) = E_{\eta}(M_{IF}(g(\mu,\eta),\xi)) + \Omega^{-1}$$

- Two methods
  - Simulate η to compute E_{η} by Monte-Carlo simulation (MC)
  - First-order (FO) linearization of the model proposed by Merlé *et al* in 1995
    - for additive random effects

$$M_{BF}(\xi) = F(\mu,\xi)^T \Sigma(\mu,\xi)^{-1} F(\mu,\xi) + \Omega^{-1}$$

    - for exponential random effects

$$M_{BF}(\xi) = \mathrm{M}^T F(\mu,\xi)^T \Sigma(\mu,\xi)^{-1} F(\mu,\xi)\mathrm{M} + \Omega^{-1}$$

$$\text{with } \mathrm{M} = \mathrm{diag}(\mu_1, \ldots, \mu_p)$$

Merlé Y, Mentré F. Bayesian design criteria: computation, comparison and application to a pharmacokinetic and a pharmacodynamic model. *J Pharmacokinet Biopharm*, 1995;23(1):101-25

Materials and methods

Shrinkage prediction

- Based on the Bayesian Fisher information Matrix
- Inspired from linear mixed effect methodology developed by Fedorov
- Extended for nonlinear mixed effects models, using M_{BF} computed by FO

$$W(\xi) = M_{BF}(\xi)^{-1}\Omega^{-1}$$

with $W(\xi)$: normalized variance of estimation

I - W used for prediction of shrinkage

Fedorov F. Mixed models: design of experiments. Presented at Isaac Newton Institute for Mathematical science, Design and Analysis of Experiment, Cambridge, UK. August 2011

Combes F, Retout S, Frey N, Mentré F. Prediction of shrinkage of individual parameters using the Bayesian information matrix in nonlinear mixed-effect models with application in pharmacokinetics. PAGE (Population Approach Group in Europe) 2012; Abstr 2442, [www.page-meeting.org/?abstract=2442]

Materials and methods

Simulation and estimation

- Evaluation of population parameter estimation with FOCEI and SAEM
  - Relative error (%) $RE = \frac{\hat{\mu}-\mu}{\mu} \times 100$
  - Bias expressed as the mean RE on the 1000 vectors of estimated parameters
  - Root mean square error $RMSE = \sqrt{E(\hat{\mu}-\mu)^2}$

Results

Algorithm performance

Scenario 1, under H_0; 500 subjects

		2 samples per subject		3 samples per subject		5 samples per subject	
	(%)	FOCE	SAEM	FOCE	SAEM	FOCE	SAEM
ka	**bias**	1.6	0.2	-6.2	0.6	-5.0	0.5
	RMSE	11.2	10.6	8.8	6.7	7.0	5.6
V	**bias**	**12.4**	-0.4	5.2	0.1	4.6	0.1
	RMSE	15.5	7.4	7.5	5.1	6.2	4.3
CL	**bias**	**15.4**	0.2	**13.9**	-0.0	**10.4**	0.0
	RMSE	15.9	3.4	14.2	2.7	10.7	2.5
ω^2_{ka}	**bias**	**10.9**	6.3	**12.7**	-0.8	-6.8	-1.7
	RMSE	43.4	46.8	31.4	31.5	22.7	23.9
ω^2_{V}	**bias**	4.7	-1.9	-6.3	0.3	-2.1	0.1
	RMSE	22.7	23.0	16.5	15.3	11.6	11.4
ω^2_{CL}	**bias**	9.8	1.8	0.8	0.4	-1.1	0.1
	RMSE	23.1	13.9	10.9	10.3	8.1	8.4
σ_{inter}	**bias**	**27.0**	-0.6	**20.0**	0.1	9.4	-0.0
	RMSE	30.1	12.1	22.4	9.2	12.1	7.3
σ_{slope}	**bias**	**-19.0**	-1.4	**-10.0**	-0.2	-2.9	0.0
	RMSE	23.8	9.5	11.7	5.6	4.5	3.5

- SAEM less biased and less spread than FOCE in all cases

Results

Algorithm performance

Scenario 2, under H_0; 500 subjects

		2 samples per subject		3 samples per subject		5 samples per subject	
	(%)	FOCE	SAEM	FOCE	SAEM	FOCE	SAEM
ka	**bias**	-5.2	-1.0	-6.9	-1.4	-5.2	-0.7
	RMSE	12.0	7.5	13.1	6.0	7.4	5.2
V	**bias**	-1.4	-1.0	-2.6	-1.1	-1.0	-0.6
	RMSE	8.7	5.0	10.3	4.2	3.5	3.4
CL	**bias**	**15.4**	0.2	**13.9**	-0.0	**10.4**	0.0
	RMSE	15.9	3.4	14.2	2.7	10.7	2.5
ω^2_{ka}	**bias**	**21.9**	**51.9**	**17.3**	**37.0**	-5.1	**22.8**
	RMSE	82.8	99.6	73.2	85.2	52.3	67.0
ω^2_{V}	**bias**	**-55.3**	**-18.1**	**-44.1**	**-12.5**	**-23.0**	-8.2
	RMSE	67.7	51.9	57.8	38.7	31.8	28.5
ω^2_{CL}	**bias**	**-30.9**	3.3	**-26.3**	1.4	**-10.3**	0.9
	RMSE	41.3	30.9	35.2	23.6	20.1	16.1
σ_{inter}	**bias**	**33.5**	-0.6	**33.3**	0.2	**23.5**	-0.1
	RMSE	36.6	17.6	35.4	14.4	26.0	12.7
σ_{slope}	**bias**	-3.7	-0.4	-4.5	-0.4	-3.3	-0.2
	RMSE	7.1	6.1	6.5	4.8	4.8	3.7

- SAEM less biased and less spread than FOCE in all cases

Partial results - 1

algorithm		FOCE	SAEM
Design	β	**0**	
Scenario 1			
2	LRT	5	3.8
	CT	3.5	3.9
3	LRT	4.7	4.6
	CT	3.6	4.3
5	LRT	4.2	4.8
	CT	3.5	4.7
Scenario 2			
	β	**0**	
2	LRT	5.5	4.2
	CT	3.7	4.0
3	LRT	7.0	4.6
	CT	4.7	4.9
5	LRT	5.8	5.0
	CT	4.2	5.0

Algorithms

NONMEM

FOCEI: default options

SAEM - Expert:

- SAEM INTERACTION NBURN=15000 ISAMPLE=3 **NITER=5000** SIGL=8 CTYPE=3 PRINT=50 CINTERVAL=100

ITS - naive: default options

ITS - expert:

- ITS INTERACTION NITER=3000 SIGL=8 PRINT=50 CTYPE=3

ITS_SAEM - expert:

- ITS INTERACTION NITER=3000 SIGL=8 PRINT=50 CTYPE=3
- SAEM INTERACTION NBURN=15000 ISAMPLE=3 **NITER=2500** SIGL=8 CTYPE=3 PRINT=50 CINTERVAL=100

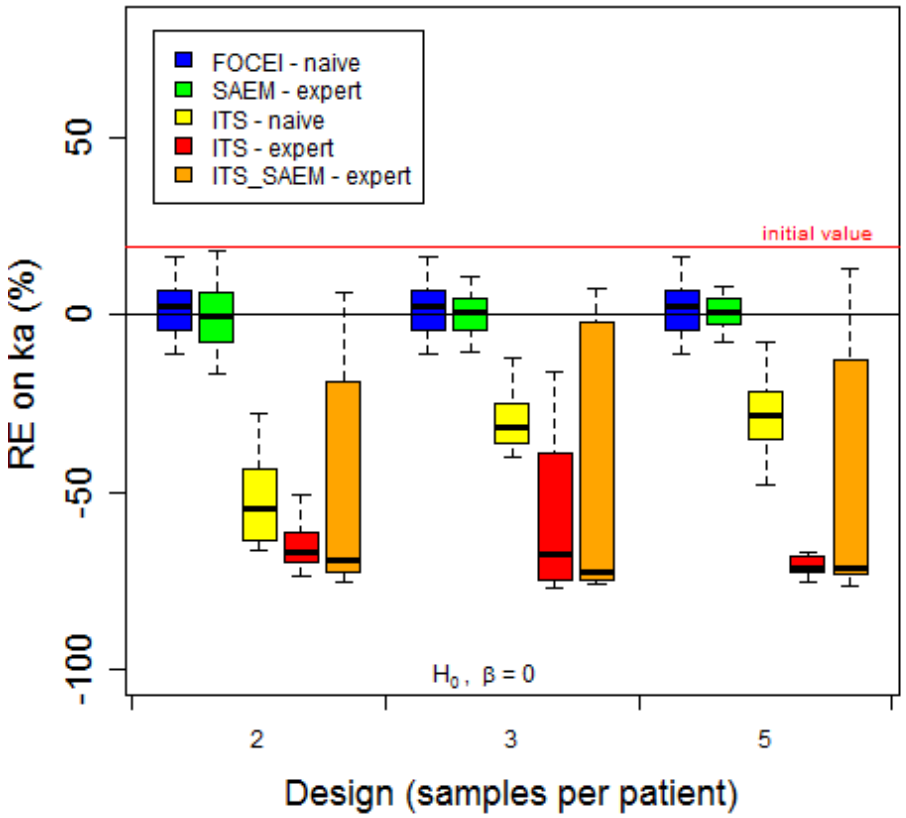
N = 500 subjects

R = 100 replicates

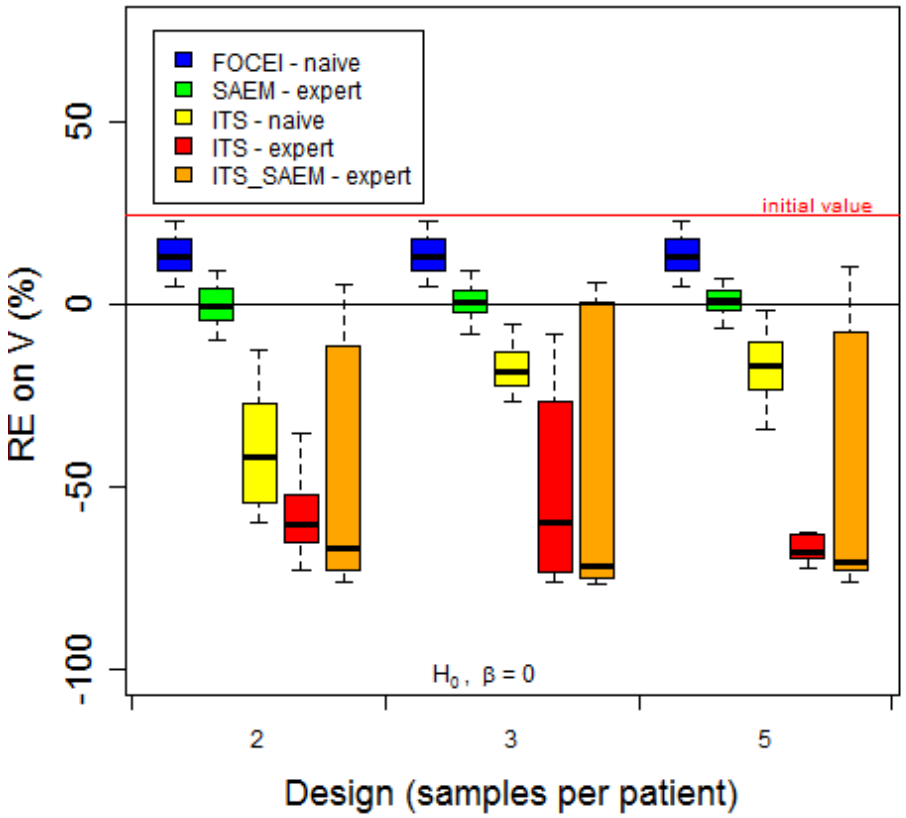
Scenario 1

* L Gibianski, E Gibianski, R Bauer, Pharmacokinet Pharmacodyn. 2012 Feb;39(1):17-35. Epub 2011 Nov 19.

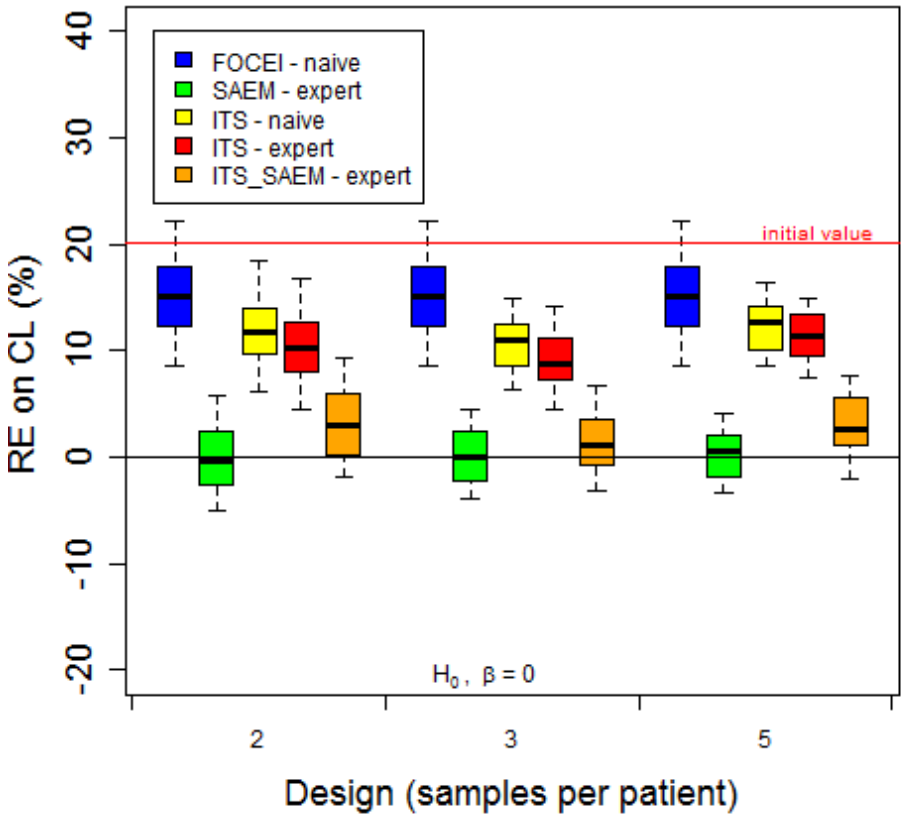
Absorption


FOCEI - naive
SAEM - expert
ITS - naive
ITS - expert
ITS_SAEM - expert
initial value
RE on ka (%)
50
0
-50
-100
H_0 , β = 0
2
3
5
Design (samples per patient)

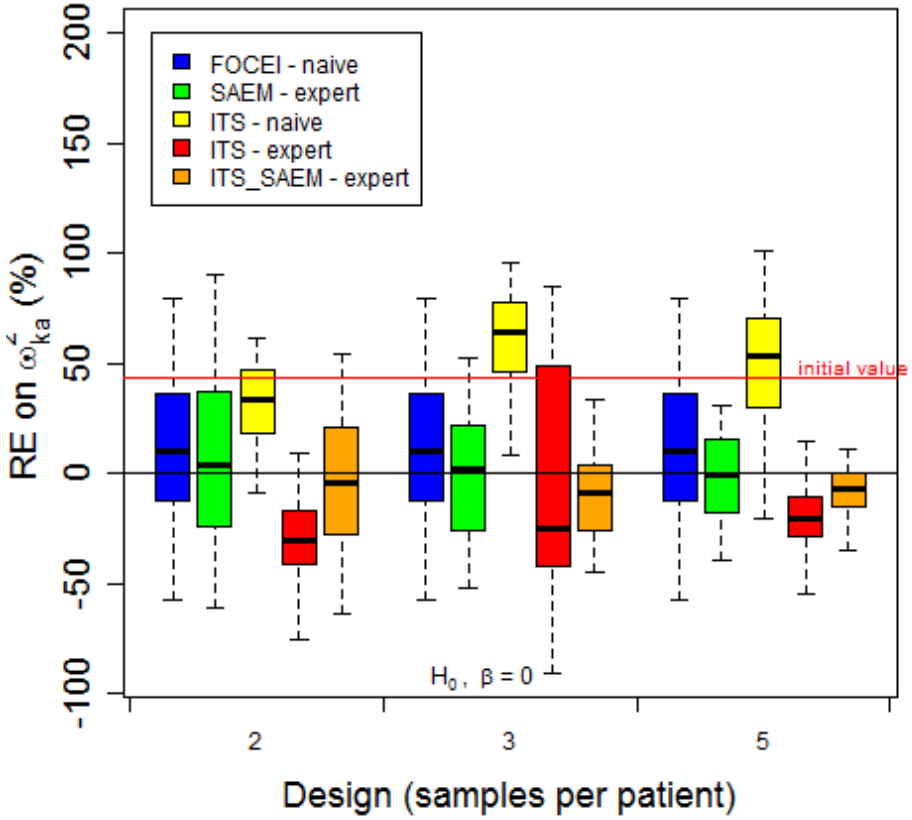
Volume


FOCEI - naive
SAEM - expert
ITS - naive
ITS - expert
ITS_SAEM - expert
initial value
RE on V (%)
50
0
-50
-100
H_0 , β = 0
2
3
5
Design (samples per patient)

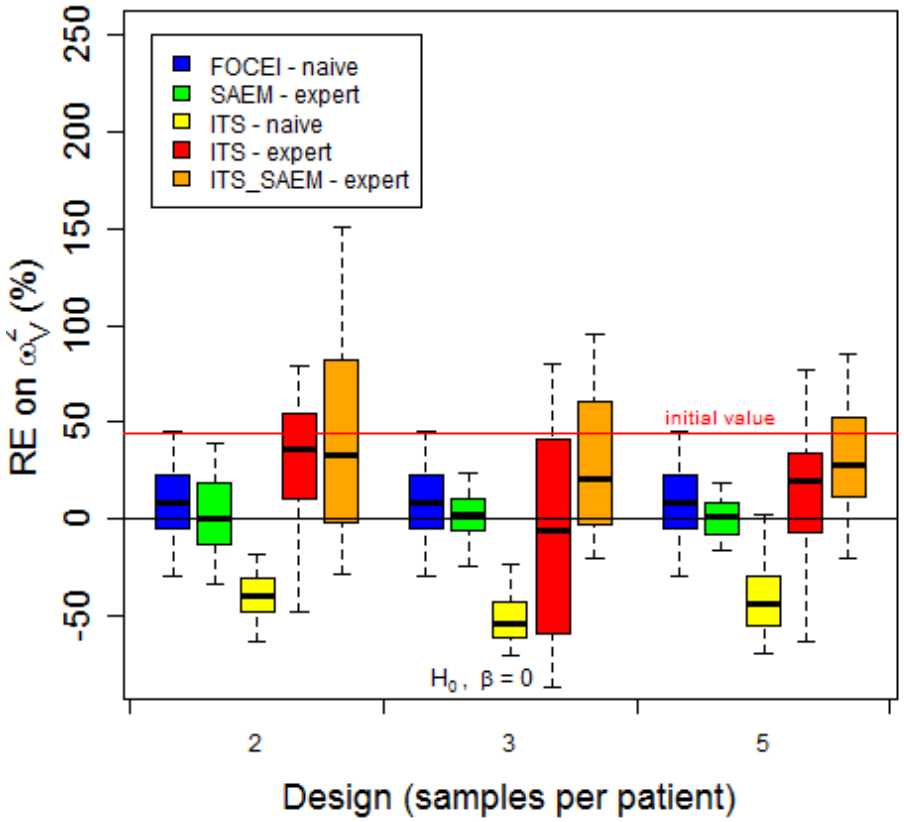
Clearance


FOCEI - naive
SAEM - expert
ITS - naive
ITS - expert
ITS_SAEM - expert
initial value
RE on CL (%)
40
30
20
10
0
-10
-20
H_0 , β = 0
2
3
5
Design (samples per patient)

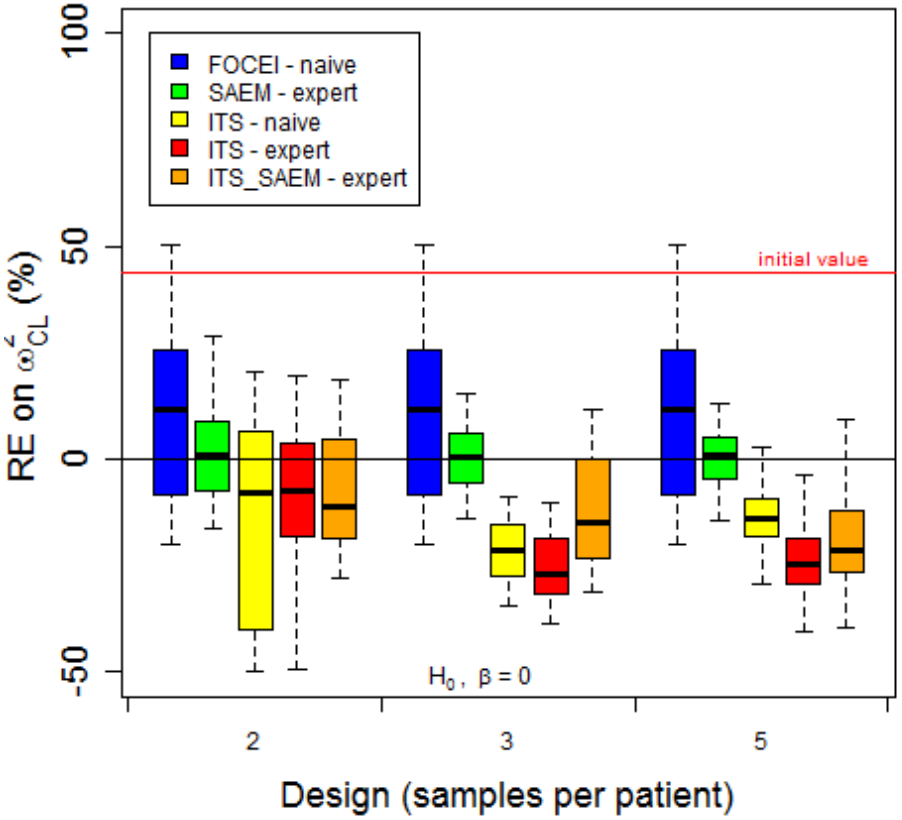
Random effects – ka



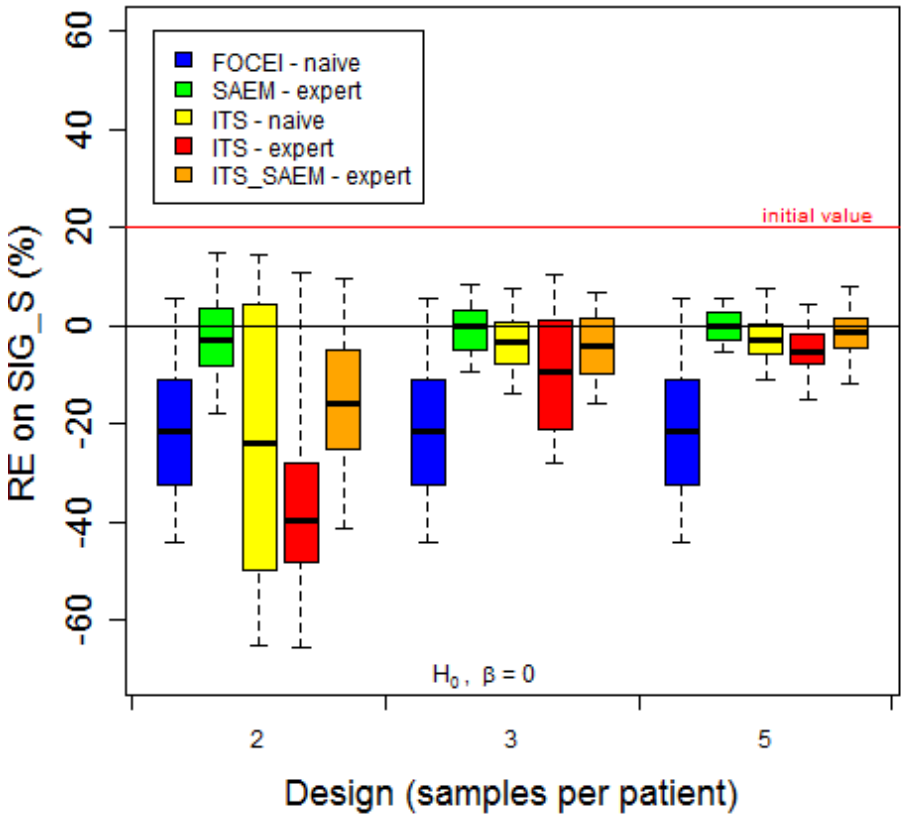
Random effects – V



Random effects – CL



Residual error – σ_{slope}



Residual error – σ_{inter}