Sample size Re-estimation and Bias

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Frank Miller, Stockholm University, Sweden

Partly joint work with
Tim Friede, Dept. of Medical Statistics,
University Medical Center Göttingen, Germany

Content

- Sample size re-estimation, bias and correction
- Continuous variance monitoring
- Blinded continuous variance monitoring
- More insight into the bias and it's consequences

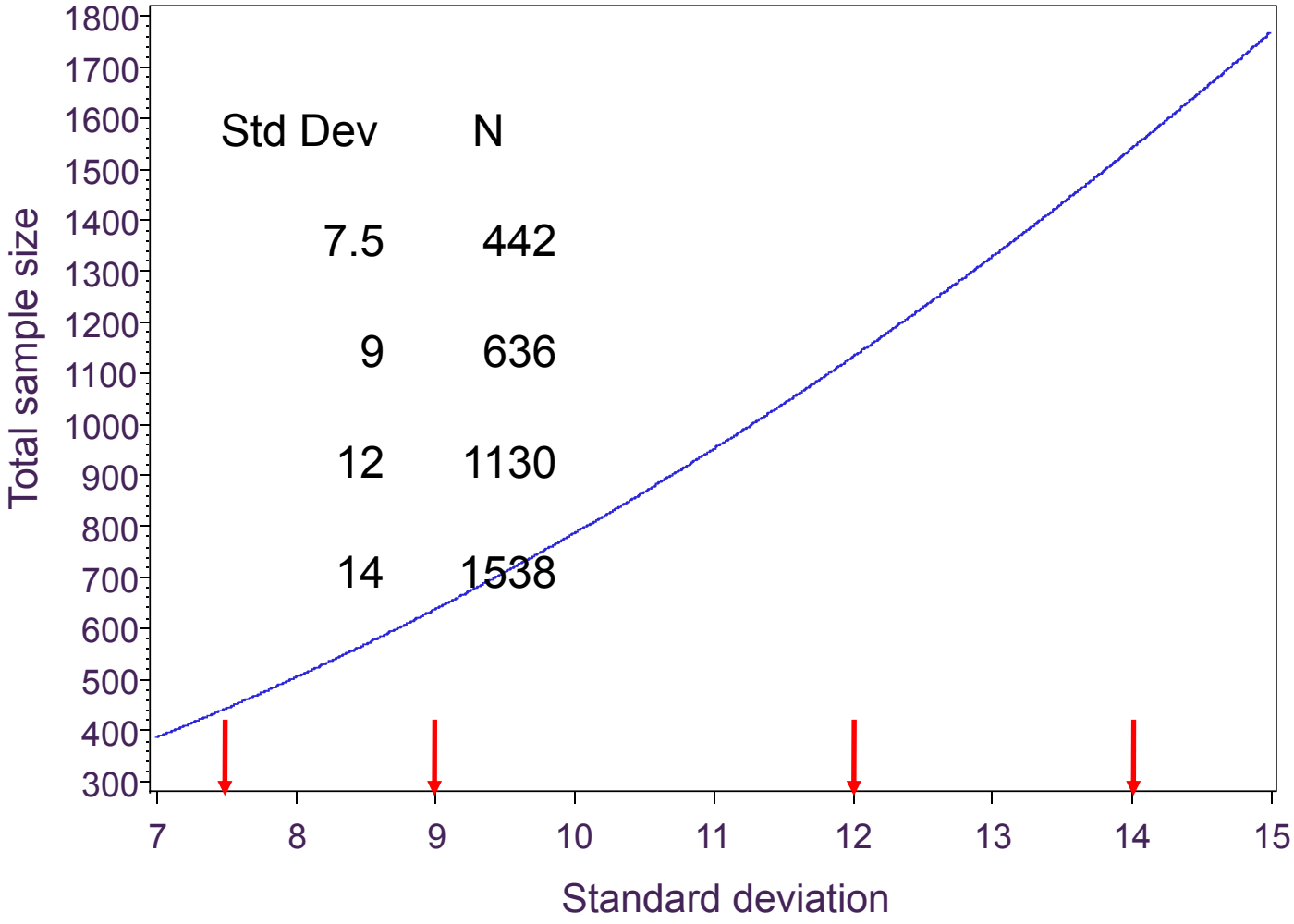
Clinical study and sample size calculation

- Randomized study comparing two treatments (e.g. new treatment versus control)
- A variable is observed which is assumed to be independently **normally distributed** with common unknown variance σ^2 and treatment difference δ
- Significance test with level α and power $1-\beta$ for $\delta = \delta_a$,
  $H_0 : \delta = 0$ (new treatment equal to control) versus
  $H_a : \delta > 0$ (new treatment better than control)
- Sample size per treatment $n = v\sigma^2,\ v = 2\left(z_{1-\alpha} + z_{1-\beta}\right)^2 / \delta_a^2$
- Since σ^2 is unknown, an initial guess required

Example: MacDonald et al. (2008)

- **Objective:** Assessment Lumiracoxib's effect on blood pressure in Osteoarthritis patients with hypertension
- **Treatments:** Lumiracoxib or Ibuprofen
- **Primary endpoint:** change from baseline at week 4 in average 24 h systolic blood pressure
- Significance level α=0.025 (1-sided), power 80% for $\delta_a = 2$ mmHg
- **Standard deviation σ= ??? mmHg**
  - White et al (2002): **9** mmHg observed (but different population)
  - Sowers et al (2005): assumed **7.5**, observed **12** mmHg (6 week follow-up)
  - Other studies in non-OA population: up to **14** mmHg

Uncertainty in the planning phase



Uncertainty about variance

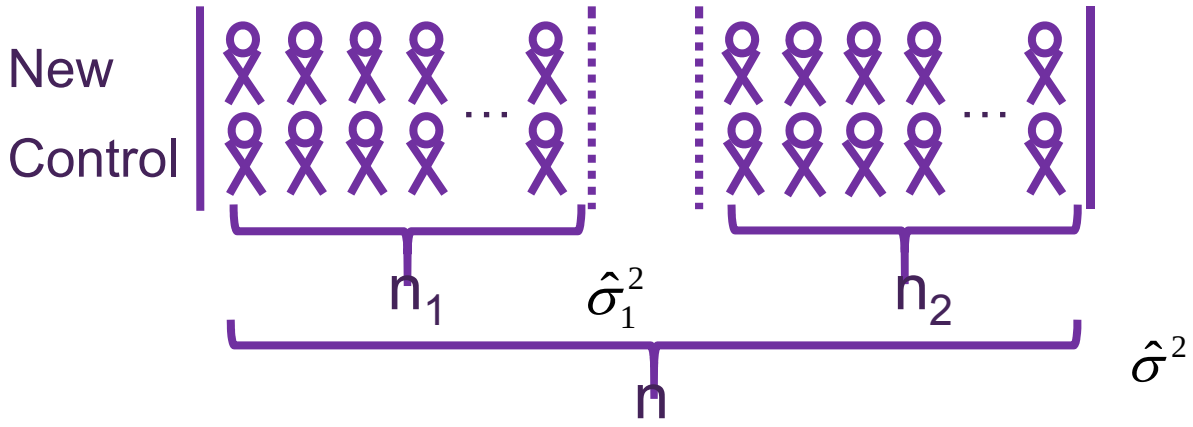
- Problem: Often considerable uncertainty regarding the variance
- Solutions include:
  - **One interim look**: estimate σ^2 from accruing data in an interim sample size review and use this estimate to adjust sample size
  - **Several interim looks** with update of variance estimate and sample size
  - **Continuous monitoring** of the variance

Sample size based on one interim analysis

Observe n_1 patients ("Stage 1") & estimate variance: $\hat{\sigma}_1^2$

Final sample size $n = v\hat{\sigma}_1^2$

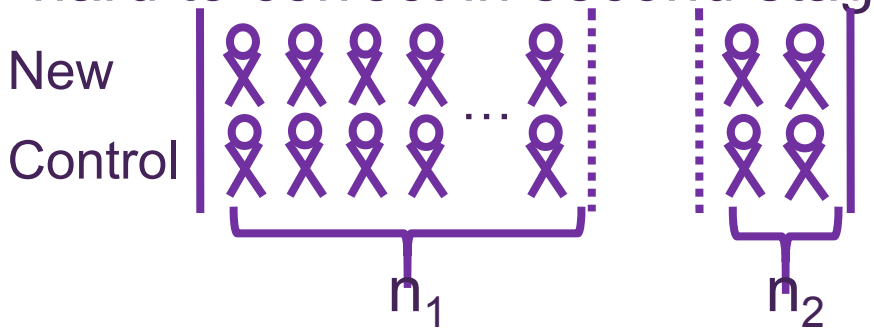
Observe additional n_2=n-n_1 patients ("Stage 2")



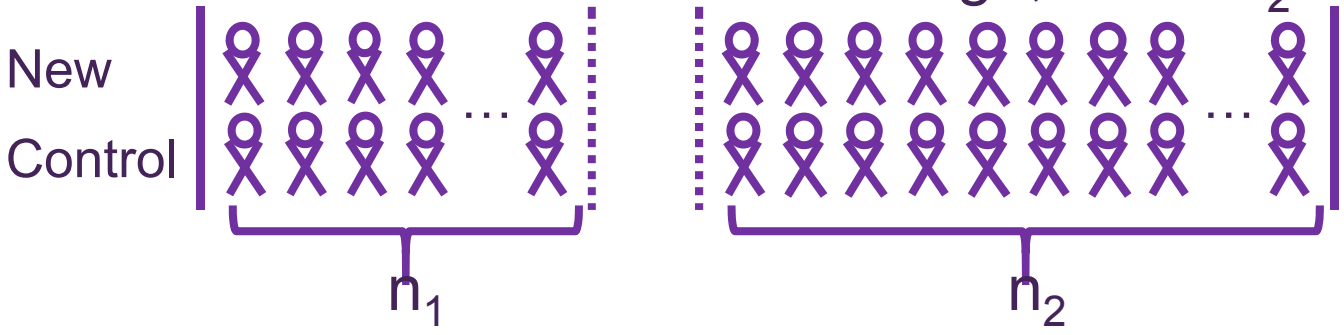
- The variance estimator $\hat{\sigma}^2$ at the end of the trial is biased. It underestimates the true variance!

Why is there a bias?

$\hat{\sigma}_1^2$ lower than true σ^2
$\rightarrow$ hard to correct in second stage, since n_2 low



- $\hat{\sigma}_1^2$ larger than true σ^2
  $\rightarrow$ easier to correct in second stage, since n_2 large



➢ $\hat{\sigma}^2$ underestimates the variance

Consequence of the bias in the final variance estimator

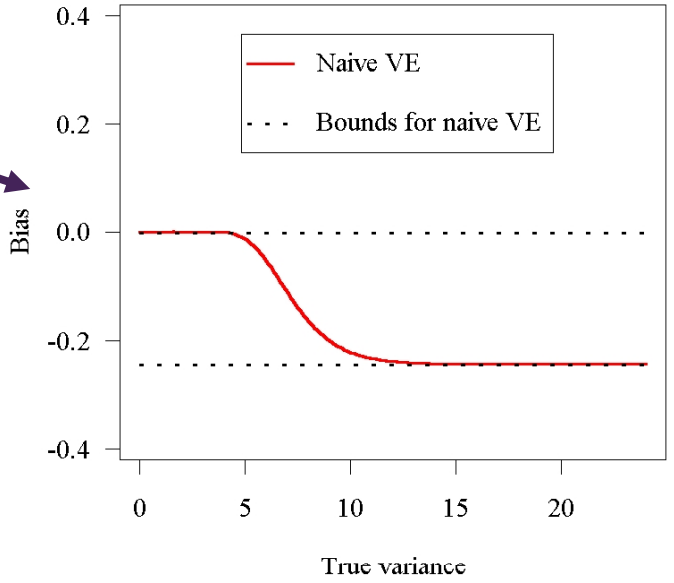
- The t-test Reject $H_0 \Leftrightarrow t > t_{2n-2,1-\alpha}$ with

  $t = \hat{\delta} \Big/ \sqrt{2\hat{\sigma}^2 / n}$ does not control the alpha level

How large is the bias?

- Bias of the ("naïve") variance estimator can be computed
- Bounds for bias (Miller, 2005)

$$-\frac{n_1-1}{n_1-2}\cdot\frac{1}{v}\le E\hat{\sigma}^2-\sigma^2\le 0$$



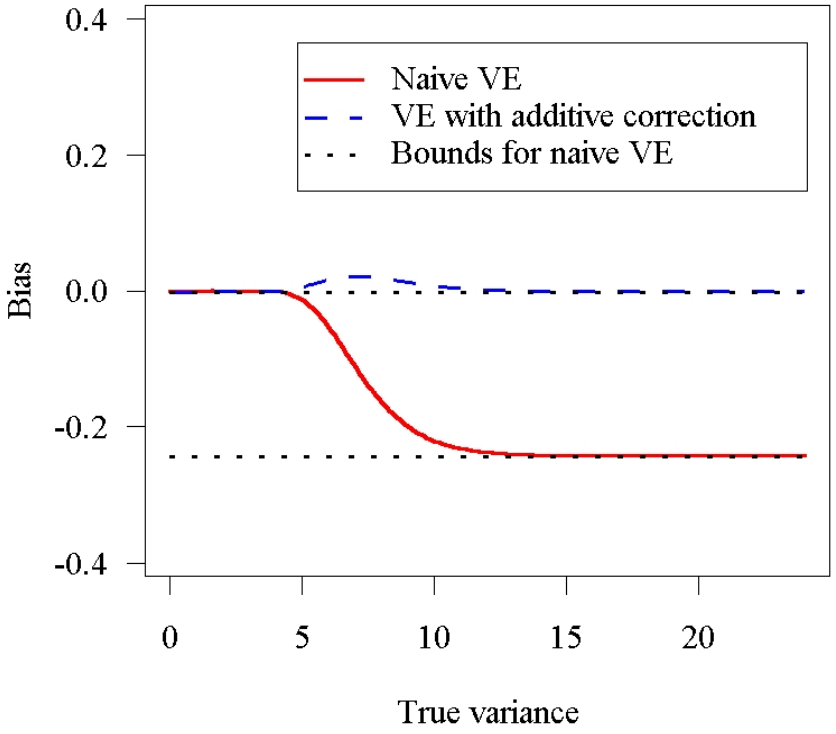
recall: $n=v\hat{\sigma}_1^2,\ v=2\left(z_{1-\alpha}+z_{1-\beta}\right)^2/\delta_a^2$

- Additive correction of final variance estimate:

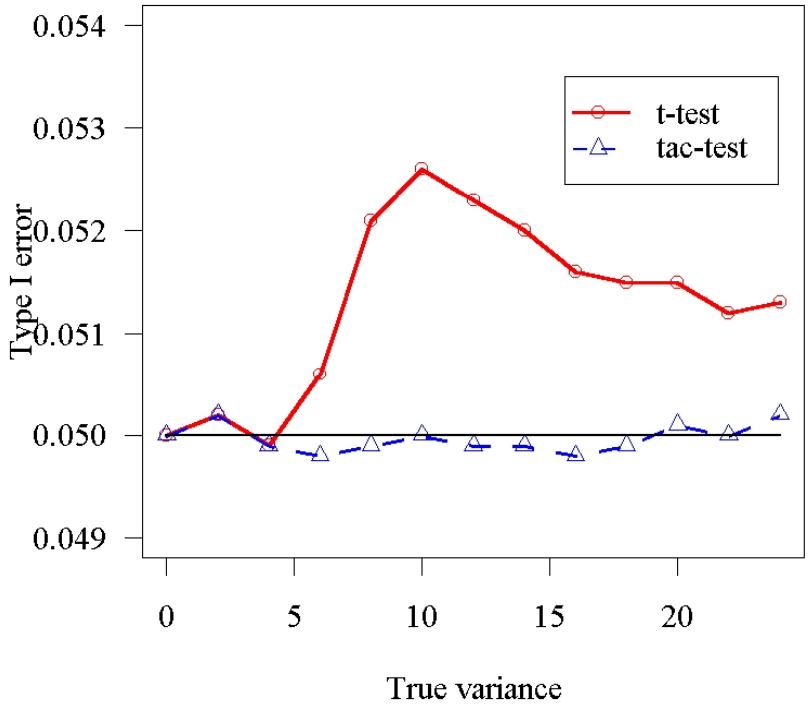
$$\hat{\sigma}_{ac}^2=\hat{\sigma}^2+\begin{cases}0, & \text{if stopped directly after interim}\\ \dfrac{n_1-1}{n_1-2}\cdot\dfrac{1}{v}, & \text{otherwise}\end{cases}$$

Correction of bias

Bias of variance estimator



Type I error of t-test and t-test with additive correction



Continuous variance monitoring

- **Continuous variance monitoring procedure**:
  - Monitor variance after each (pair of) patients: $\hat{\sigma}_n^2$ starting after n_1 patients ($n_1 \geq 2$)
  - Stop study as soon as “sample size sufficient” according to this estimate ($n \geq v\hat{\sigma}_n^2$)
- This is a stochastic process with stop-time

$$N = \min\left\{ n = n_1, n_1 + 1, \ldots \,\middle|\, \hat{\sigma}_n^2 \leq n / v \right\}$$

- Discussed in the context of clinical studies e.g. by Mehta & Tsiatis (2001) and Jennison & Turnbull (2007)
- Investigated by Friede & Miller (2012)

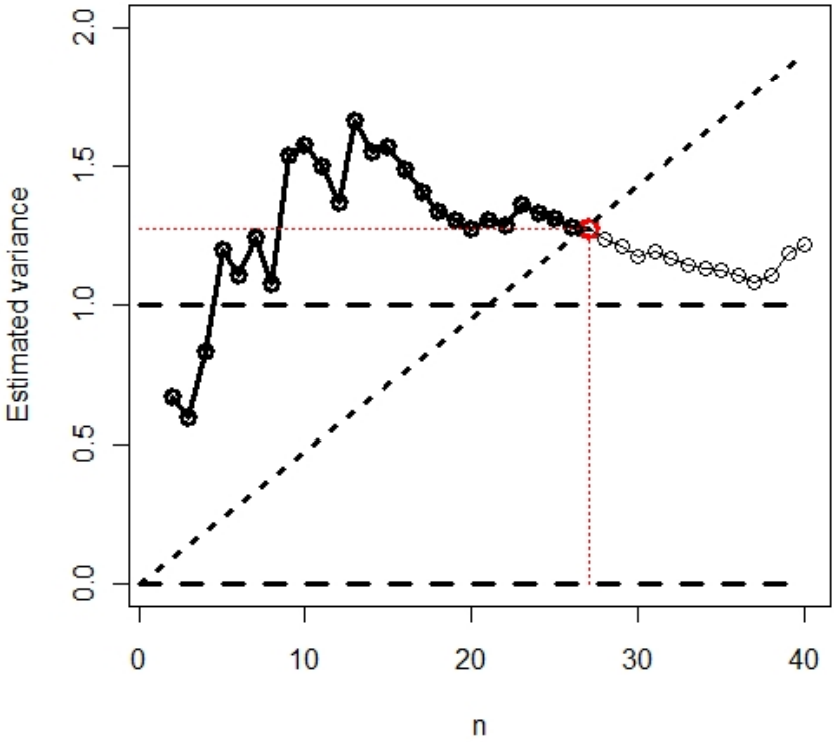
Continuous variance monitoring as stochastic process

- Example study with true variance=1, v=21

$$v = 2\left(z_{1-\alpha} + z_{1-\beta}\right)^2 \Big/ \delta_a^2$$

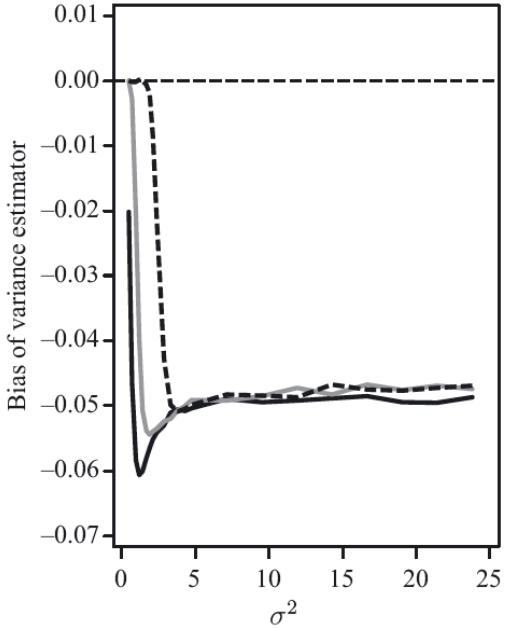
$$v = 21.0 \text{ for } \alpha = 0.025, \beta = 0.1, \delta_a = 1$$

- First time under linear boundary stops study
- $E(\hat{\sigma}_N^2) < \sigma^2 = 1$ (negative bias of variance estimator)

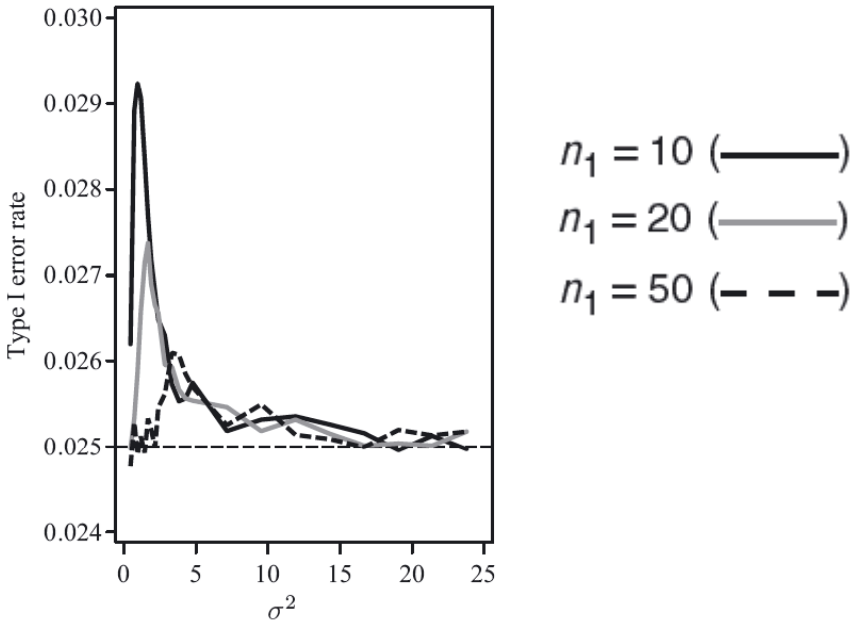


Bias of variance estimator and test

Bias of variance estimator



Bias of test size



Variance estimator $\hat{\sigma}_N^2$ at stop-time *N* negatively biased

Therefore, the t-test Reject $H_0 \Leftrightarrow t > t_{2N-2,1-\alpha}$ with $t = \hat{\delta} \Big/ \sqrt{2\hat{\sigma}_N^2 / N}$ does not control the alpha level

Blinding in clinical trials

- **Randomized clinical trials** for drug development are usually **blinded**
- Database of ongoing study has no treatment information
- Separate file with treatment info kept secretly

Database

Patient	Treatment	Result1	Result2	...
1	*	1	7.7	...
2	*	0	6.8	...
3	*	1	8.0	...
4	*	0	6.5	...
5	*	0	8.9	...

Treatments

Patient	Treatment
1	Placebo
2	Active
3	Active
4	Placebo
5	Active

Blinding and sample size re-estimation

- To perform the sample size re-estimation shown before, the **treatment of all patients needs to be known for the computation of the variance (unblinding necessary)**
- Regulatory authorities **prefer methods not requiring unblinding**

$$\hat{\sigma}_n^2 = \frac{1}{2n-2}\left(\sum_{j=1}^{n}(X_{1j}-\bar{X}_{1\bullet})^2+\sum_{j=1}^{n}(X_{2j}-\bar{X}_{2\bullet})^2\right)$$

$$\downarrow$$

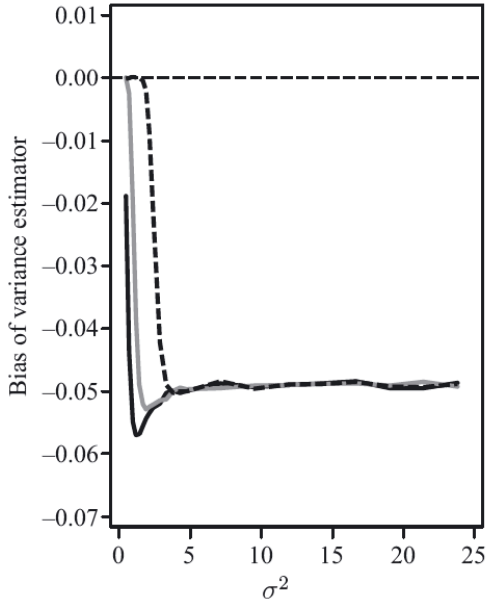
$$\hat{\sigma}_{n,\text{blind}}^2 = \frac{1}{2n-1}\left(\sum_{j=1}^{n}(X_{1j}-\bar{X}_{\bullet\bullet})^2+\sum_{j=1}^{n}(X_{2j}-\bar{X}_{\bullet\bullet})^2\right)$$

Blinded continuous monitoring

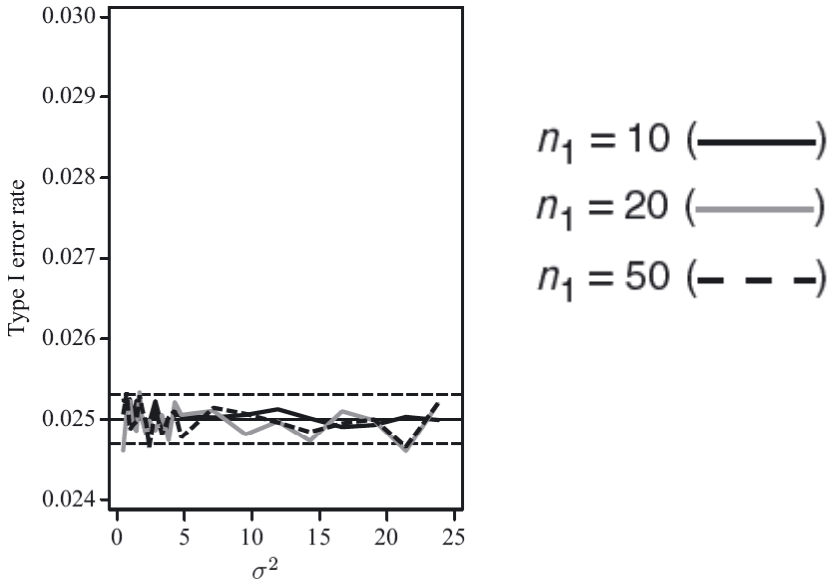
- The different sample size re-estimation procedures can be performed blinded
- Here we show the **blinded version for continuous monitoring**
- Blinded continuous monitoring procedure:
  - Monitor **overall (one sample) variance** $\hat{\sigma}^2_{n,\text{blind}}$ after each (pair of) patients, ignoring the different treatments
  - Stop study as soon as sample size sufficient according to this blinded estimate ($n \Big/ \hat{\sigma}^2_{n,\text{blind}} \geq v$)
  - Estimate final variance unblinded

Bias of variance estimator and test – blinded procedure

Bias of variance estimator

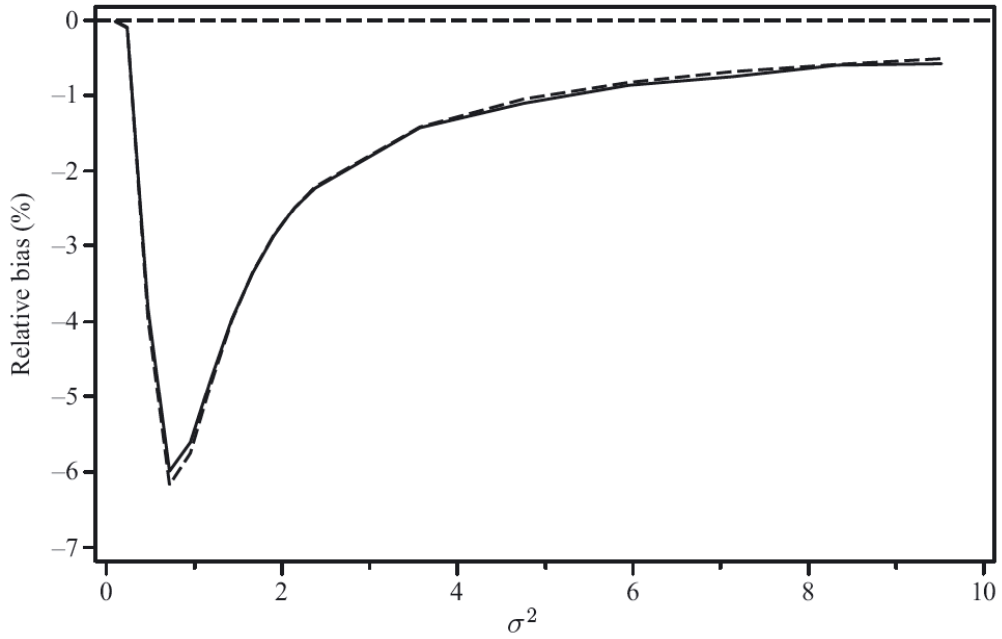


Bias of test size



Still bias for variance estimation but essentially no bias for test.

Blinded procedure: Why is the test size (almost) unbiased?



Relative bias of the numerator (———) and denominator (– – –) of the *F*-test

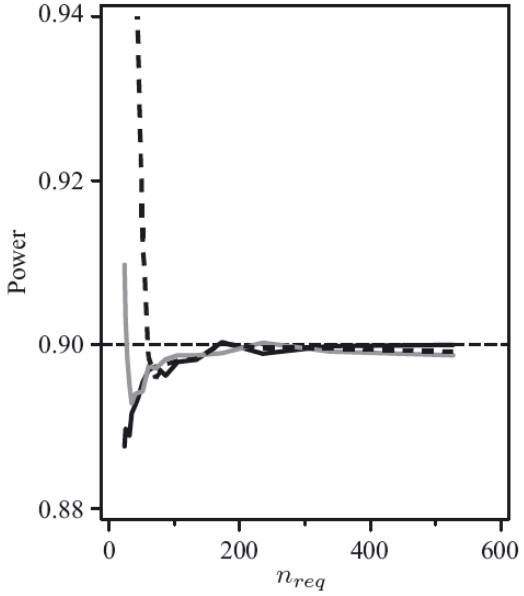
$$t = \hat{\delta}_N \Big/ \sqrt{2\hat{\sigma}_N^2 / N}$$

$$F = \frac{\frac{N}{2}\hat{\delta}_N^2}{\hat{\sigma}_N^2}$$

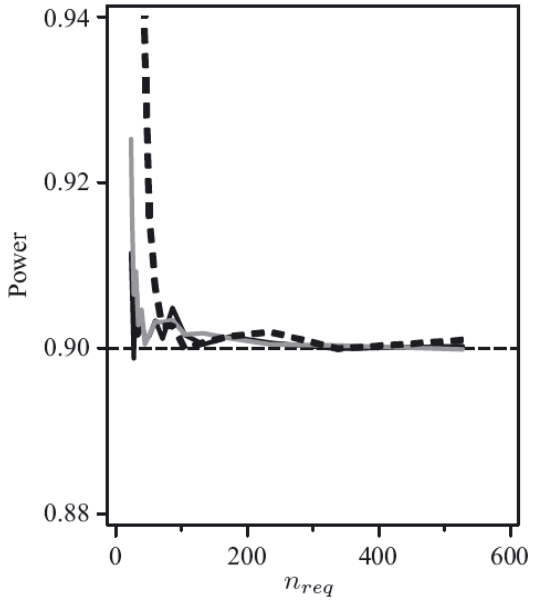
If the (two-sided) test is written as F-test, the **numerator and the denominator have the same bias** after blinded continuous monitoring

Power of test after continuous monitoring

Unblinded continuous monitoring



Blinded continuous monitoring

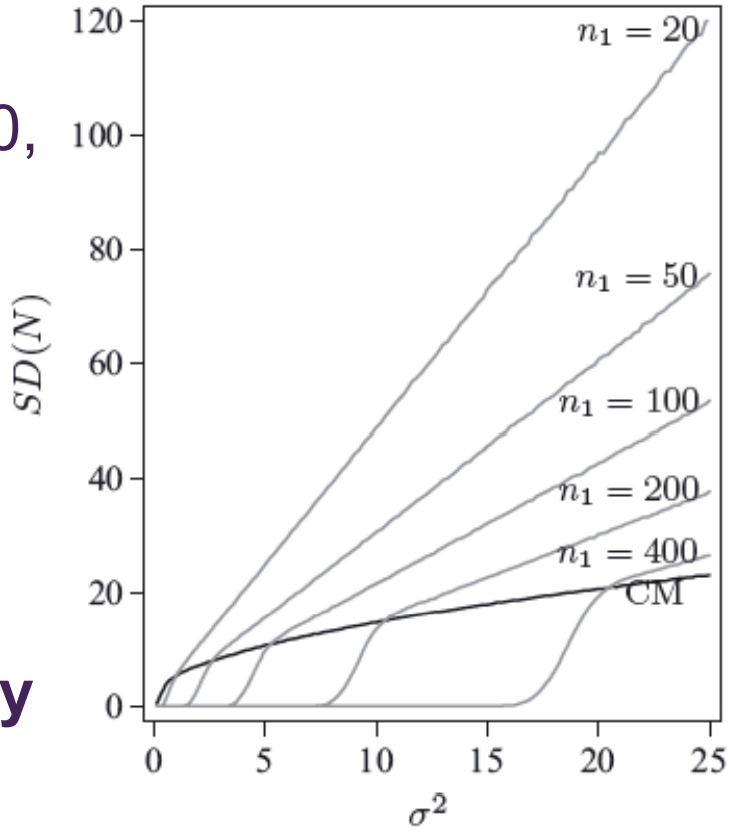


$n_1 = 10$ (——)
$n_1 = 20$ (——)
$n_1 = 50$ (– – –)

Desired power approximately maintained; better so for the blinded procedure.

Blinded procedures: Continuous monitoring versus sample size re-estimation with one interim look

- $\alpha = 0.025, 1\text{-}\beta = 0.90, \delta = \delta_a = 1$
- One look after n_1=20, 50, 100, 200, or 400 patients per treatment to estimate variance
- Compare with continuous monitoring (CM)
- If n_1 chosen too large: risk to overshoot necessary sample size
- If n_1 chosen too small: **SD for sample size can be considerably higher than for CM**



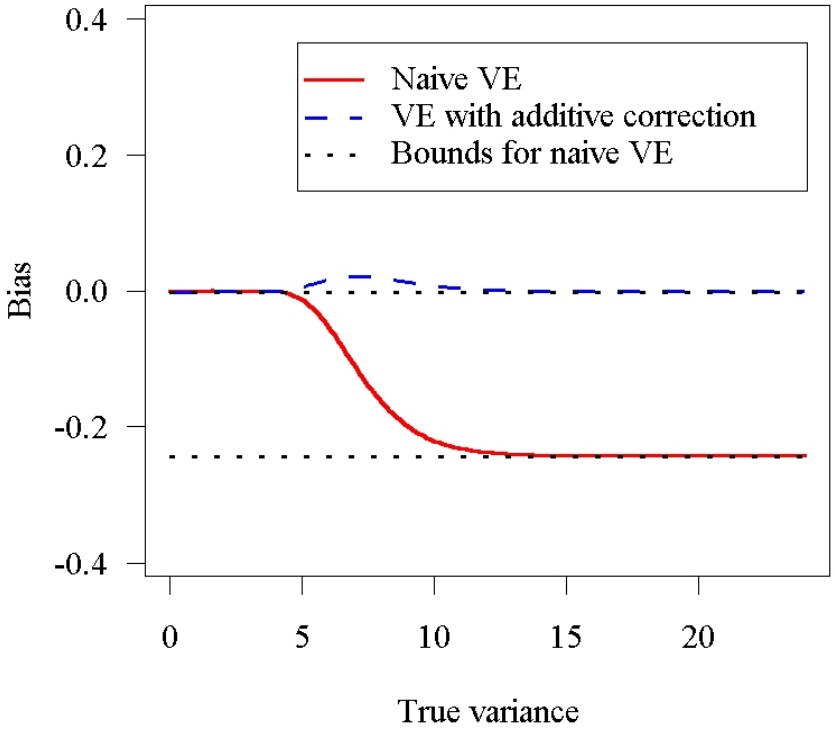
Continuous monitoring – is it logistically feasible?

- Increased use of electronic data capture techniques in clinical studies
- E.g. in chronic pain studies
  - Patients are provided with electronic diaries for their daily pain recording
  - SMS reporting has successfully been applied (Axén, Bodin, Bergström et al, 2012)
  - Pain intensity ratings can immediately be transferred to central database of sponsor

➢ Continuous monitoring feasible in some (but not all) clinical study situations

Back to the bias for sample size re-estimation with one look

Bias of variance estimator



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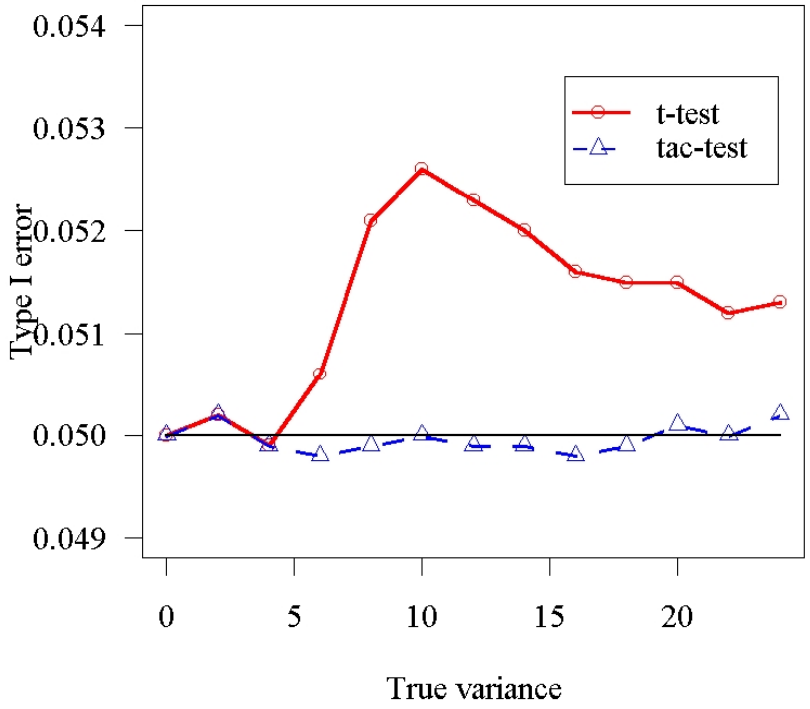
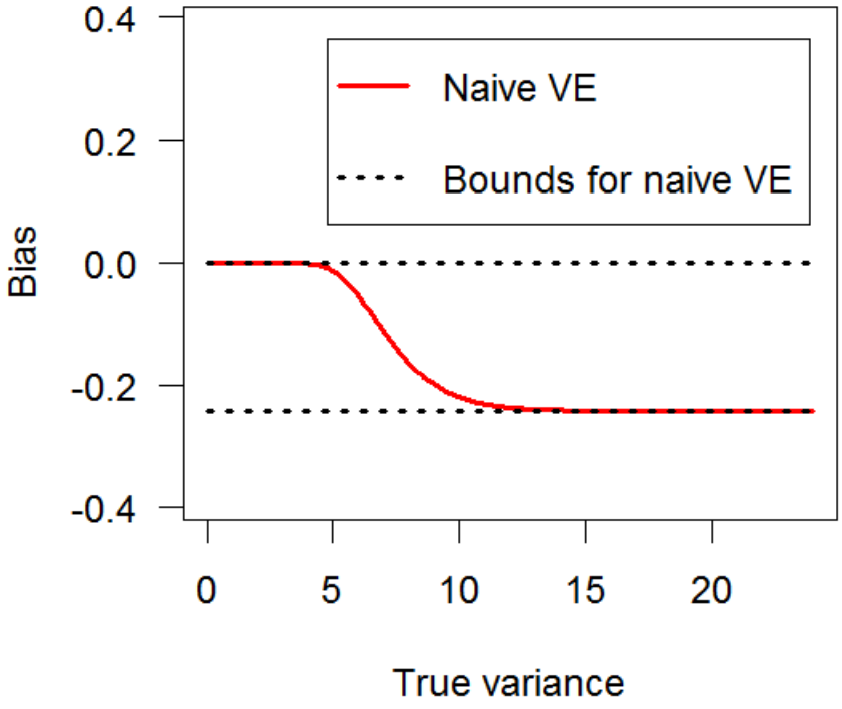


Bias for unblinded case with 1 IA

Bias of variance estimator



$$-\frac{n_1-1}{n_1-2}\cdot\frac{1}{v}\le E\hat{\sigma}^2-\sigma^2\le 0$$

Exact bias:

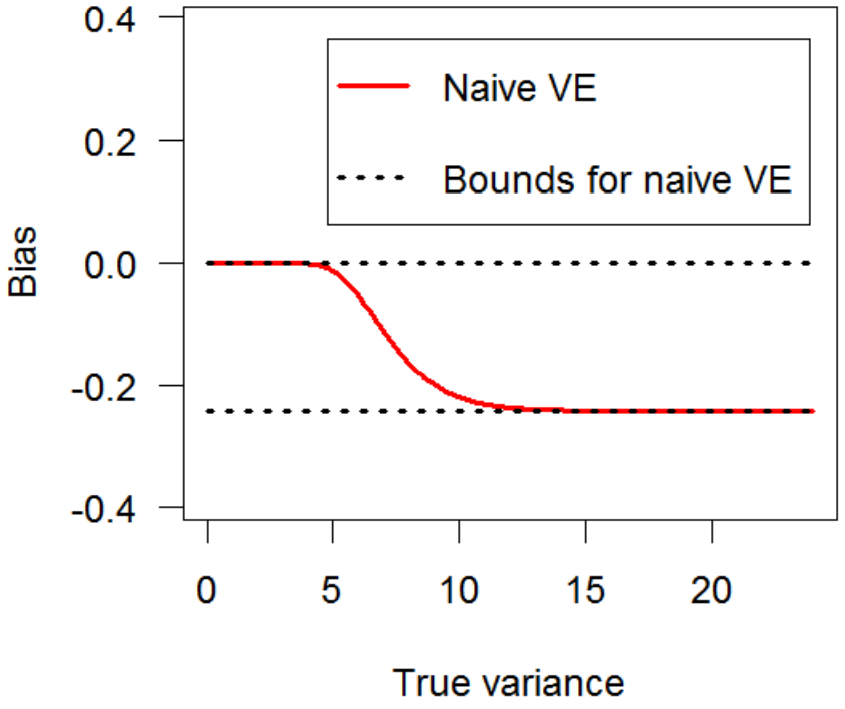
$$\frac{2(n_1-1)^2}{vd}\{F_{2n_1}(d)-F_{2n_1-2}(d)\}+\frac{n_1-1}{v}\{1-F_{2n_1-2}(d)\}$$
$$-\frac{(n_1-1)^2}{v(n_1-2)}\{1-F_{2n_1-4}(d)\}.$$

where F is the chi-square distribution function and

$$d=(2n_1-2)(n_1+n_{2\min}-1)/(v\sigma^2)$$

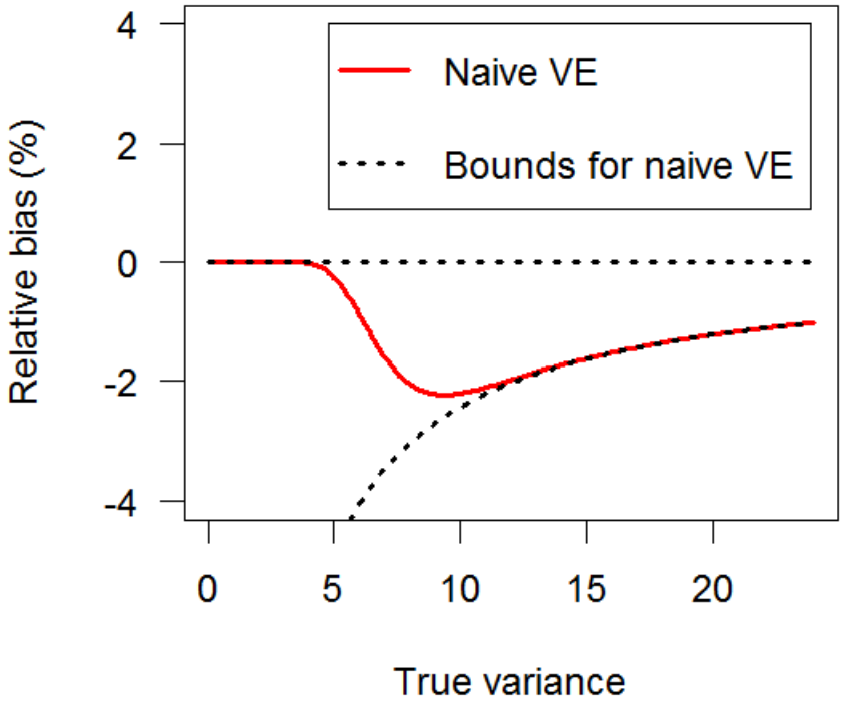
Bias for unblinded case with 1 IA

Absolute bias of variance estimator



$$-\frac{n_1-1}{n_1-2}\cdot\frac{1}{v}\le E\hat{\sigma}^2-\sigma^2\le 0$$

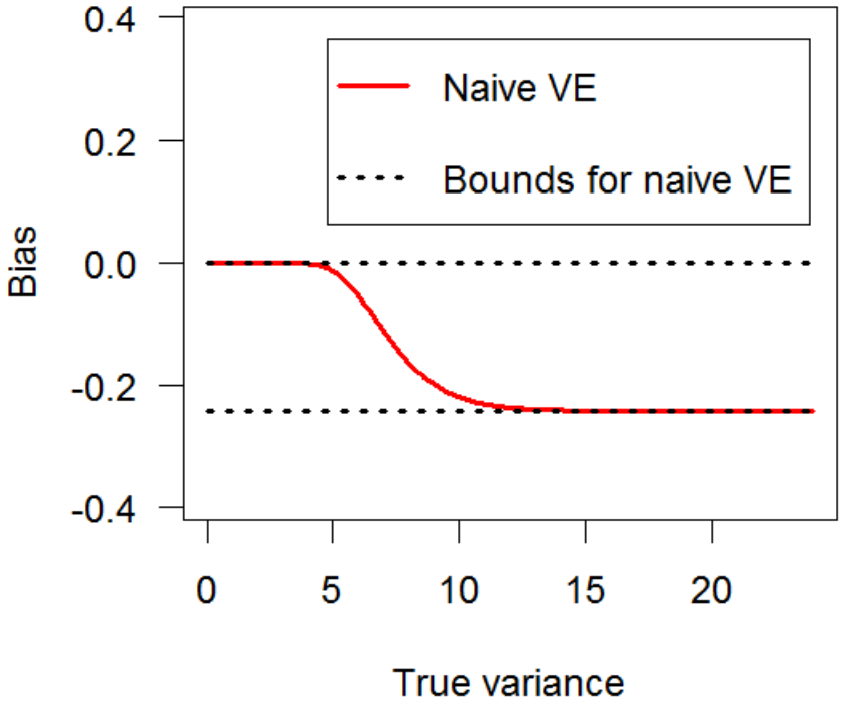
Relative bias of variance estimator



$$-\frac{n_1-1}{n_1-2}\cdot\frac{1}{v\sigma^2}\le-\frac{E\hat{\sigma}^2-\sigma^2}{\sigma^2}\le 0$$

Bias for unblinded case with 1 IA

Absolute bias of variance estimator



$$-\frac{n_1-1}{n_1-2}\cdot\frac{1}{v}\le E\hat{\sigma}^2-\sigma^2\le 0$$

Assumptions for this graph

- Sample size in first stage n_1=20 per group
- Minimum sample size in second stage: n_{2min}=10
- α=0.025, power=90%, δ_a=2.2

$$v=2\left(z_{1-\alpha}+z_{1-\beta}\right)^2\Big/\delta_a^2$$

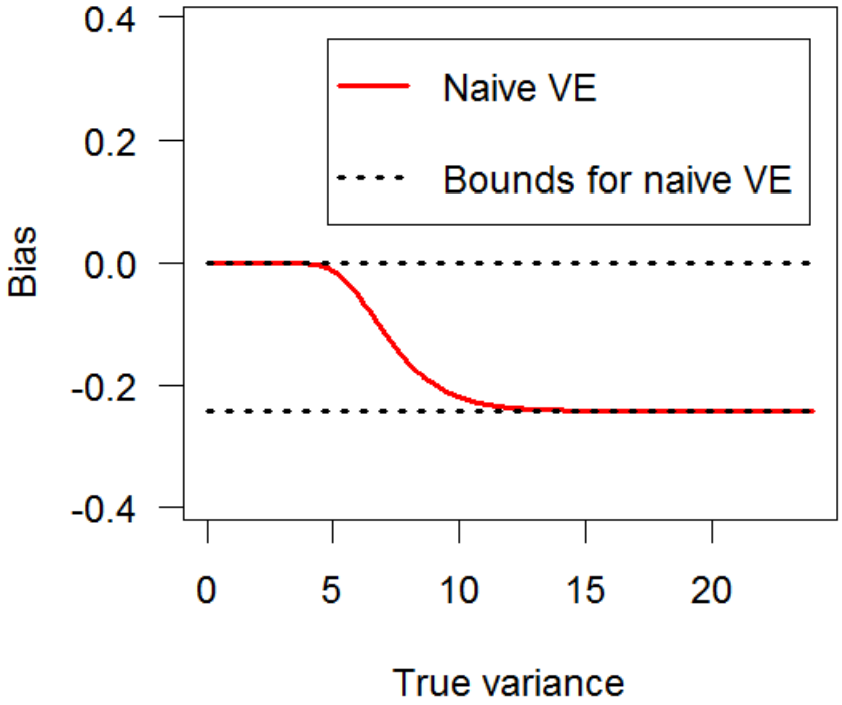
- Sample size formula for interim

$$N=\max\left\{v\hat{\sigma}_1^2+1,n_1+n_{2\min}\right\}$$

- How does the bias depend on n_{2min}, n_1, δ_a? ⊤

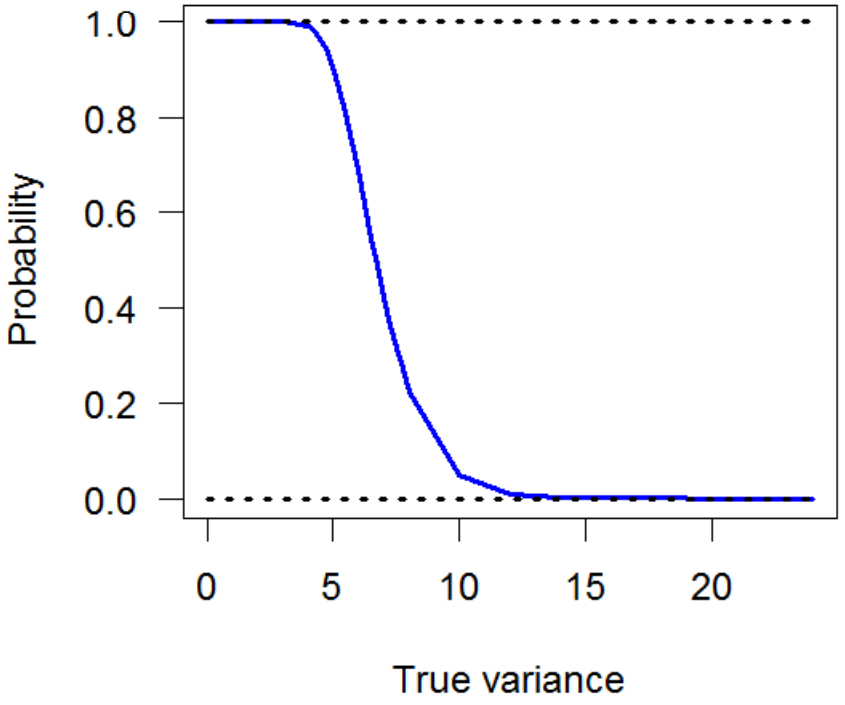
Bias for unblinded case with 1 IA

Absolute bias of variance estimator



$$E\hat{\sigma}^2 - \sigma^2$$

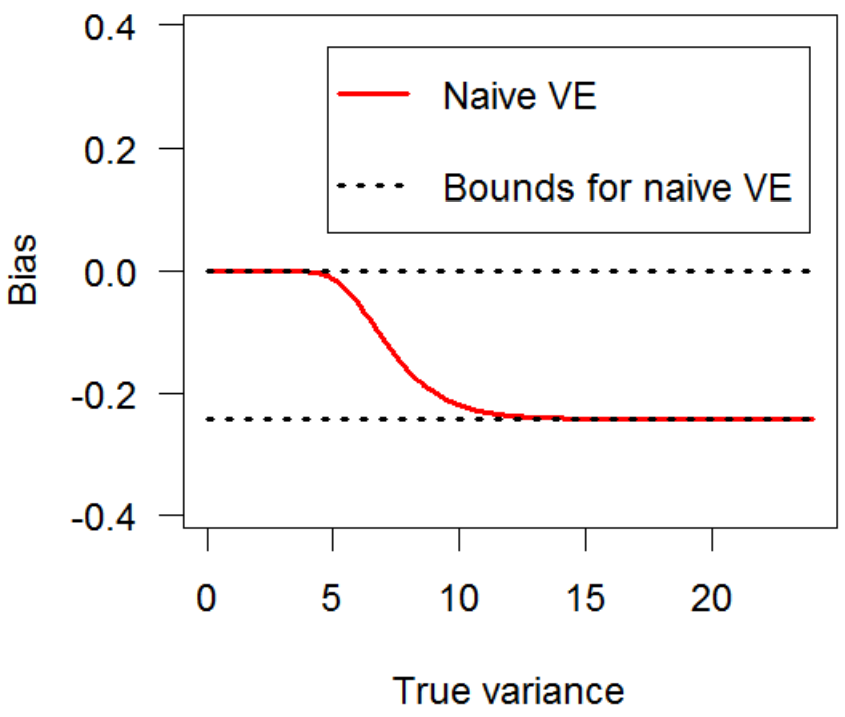
Probability for stopping the study with minimal sample size n_1+n_{2min}



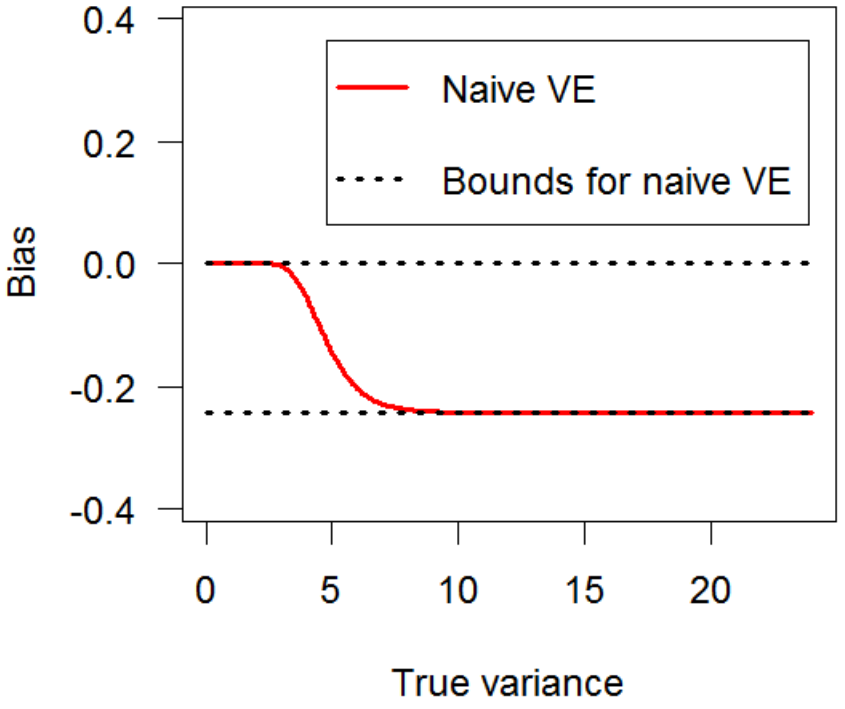
$$P(N = n_1 + n_{2\min})$$

Bias for unblinded case with 1 IA

Bias of variance estimator, n_{2min}=10

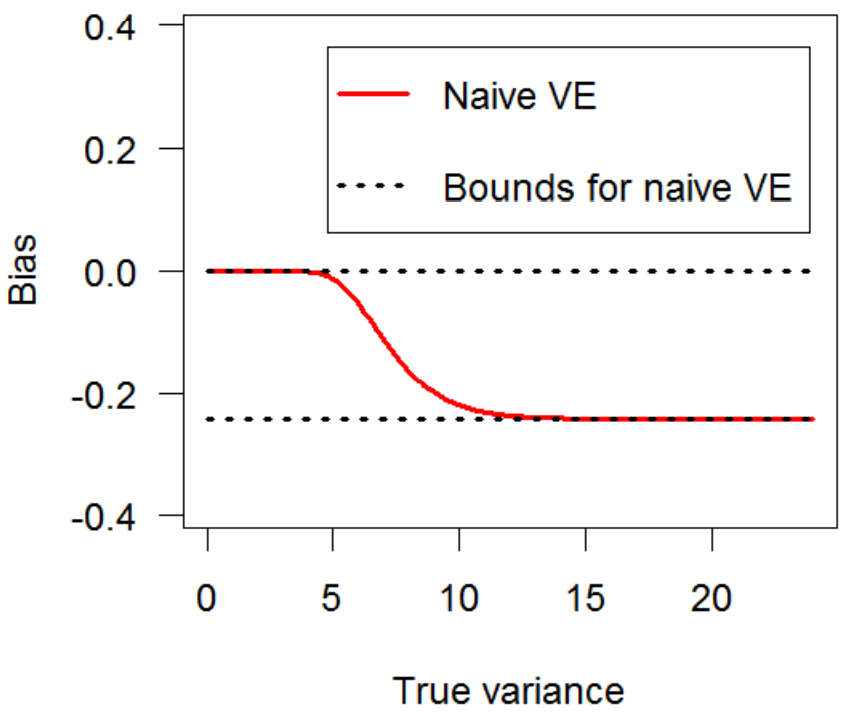


Bias of variance estimator, n_{2min}=0

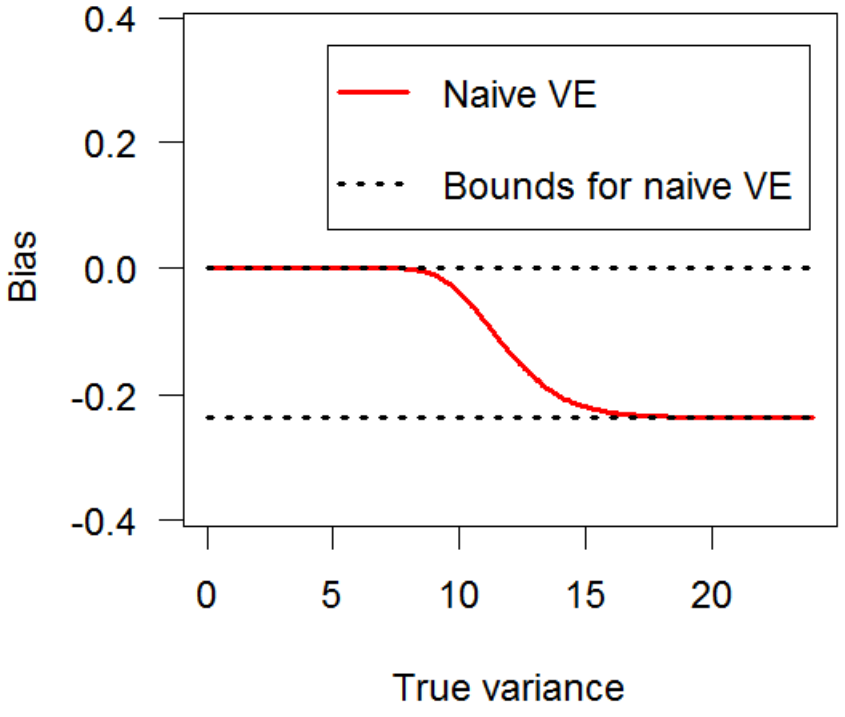


Bias for unblinded case with 1 IA

Bias of variance estimator, n_1=20

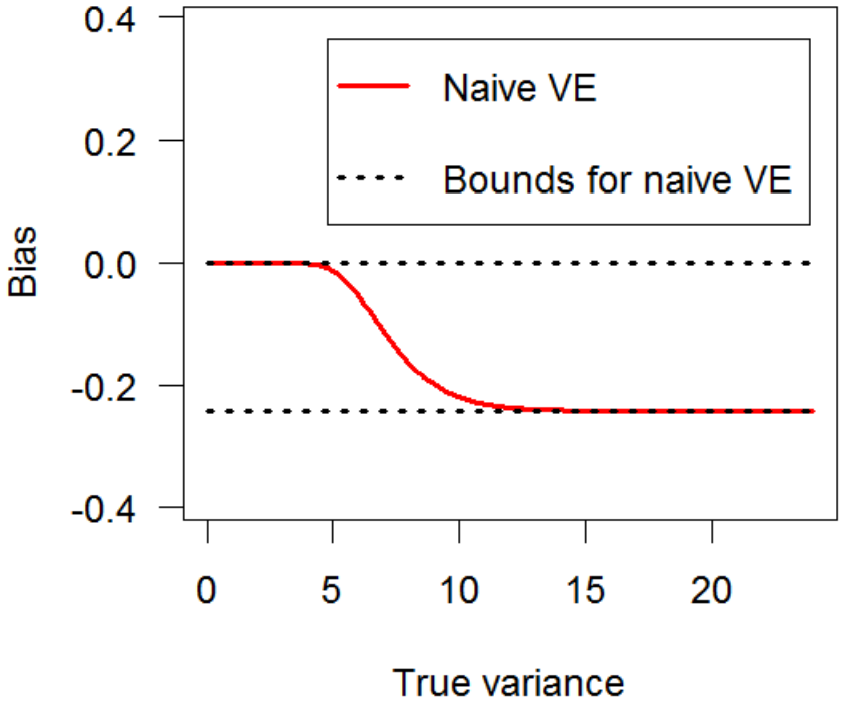


Bias of variance estimator, n_1=40

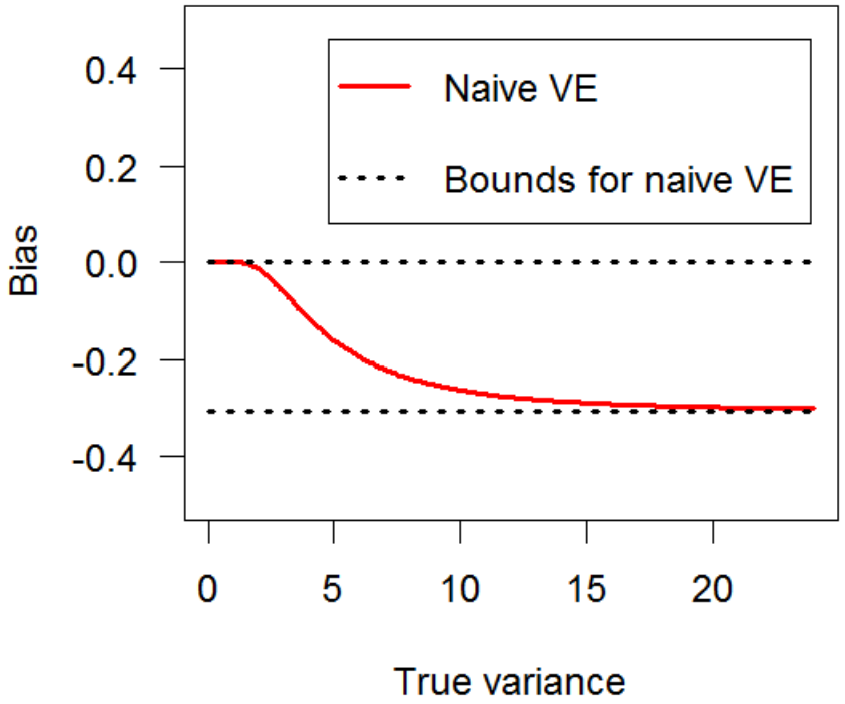


Bias for unblinded case with 1 IA

Bias of variance estimator, n_1=20

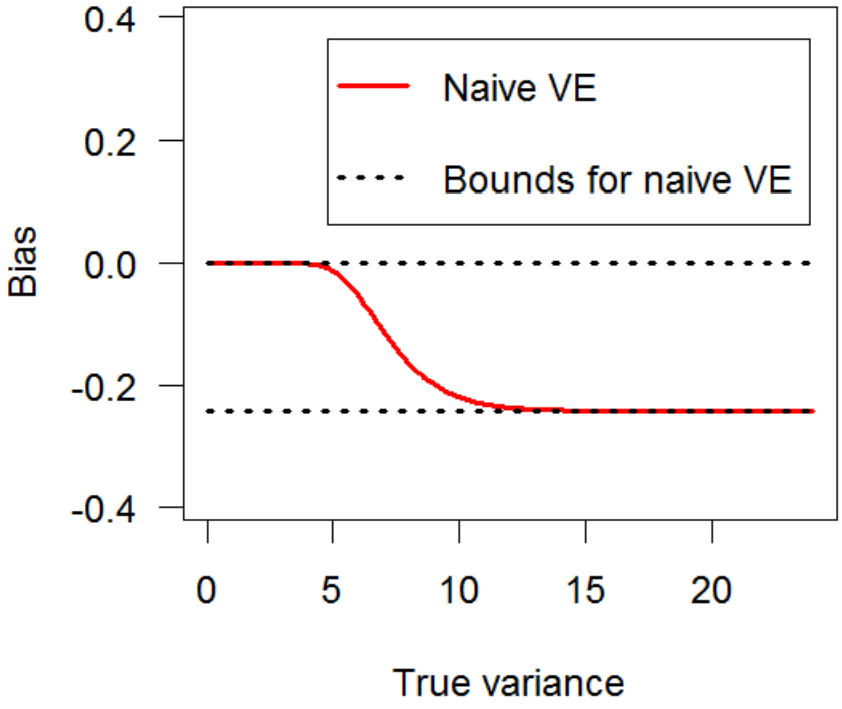


Bias of variance estimator, n_1=5

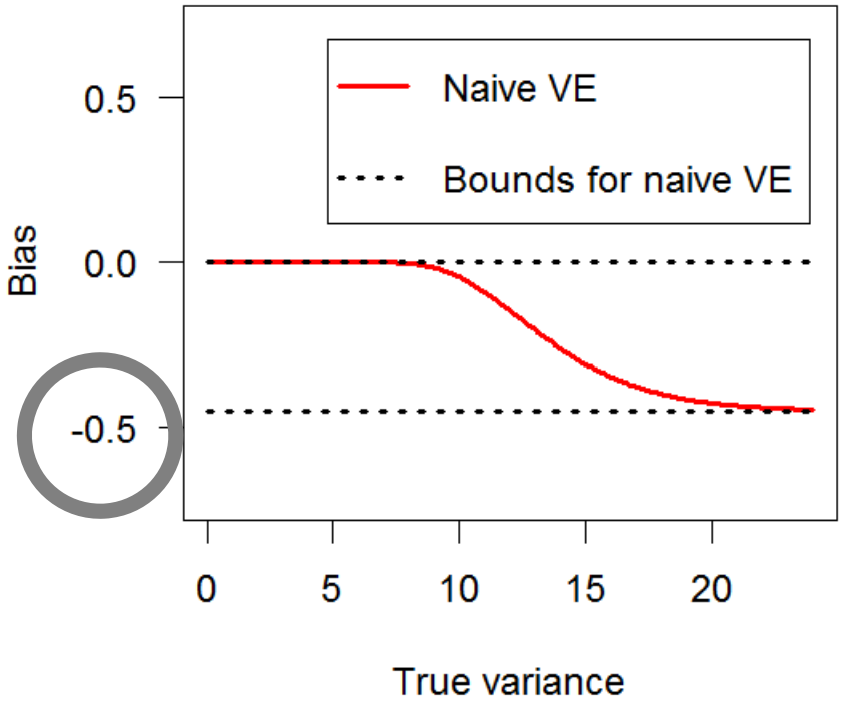


Bias for unblinded case with 1 IA

Bias of variance estimator, v=4.34
(α=0.025, β=0.1, δ_a=2.2)



Bias of variance estimator, v=2.34
(α=0.025, β=0.1, δ_a=3)



Maximal relative bias for both cases ~2.5%

Dependence of bias on parameters

- The **absolute bias** for large variances depends almost not on n_1 and not on the minimum number of patients in Stage 2
- The **relative bias** is largest if there is no minimum number of patients for Stage 2 and n_1 is small; however, decreasing n_1 to very small values (e.g. from 10 to 5) does not increase the relative bias much
- The relative bias in the considered scenarios was **at most 4%**

Summary

- Sample size re-estimation **can ensure appropriate power** (neither over- or under-powered) even under uncertainty of nuisance parameters
- The **effects on estimates and tests are usually small** and often, they might be totally acceptable
- In specific situations (small studies) it might be worth to investigate the bias further

References

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