ALGORITHMS FOR EVALUATING REFERENCE SCALED AVERAGE BIOEQUIVALENCE: POWER, BIAS AND CONSUMER RISK

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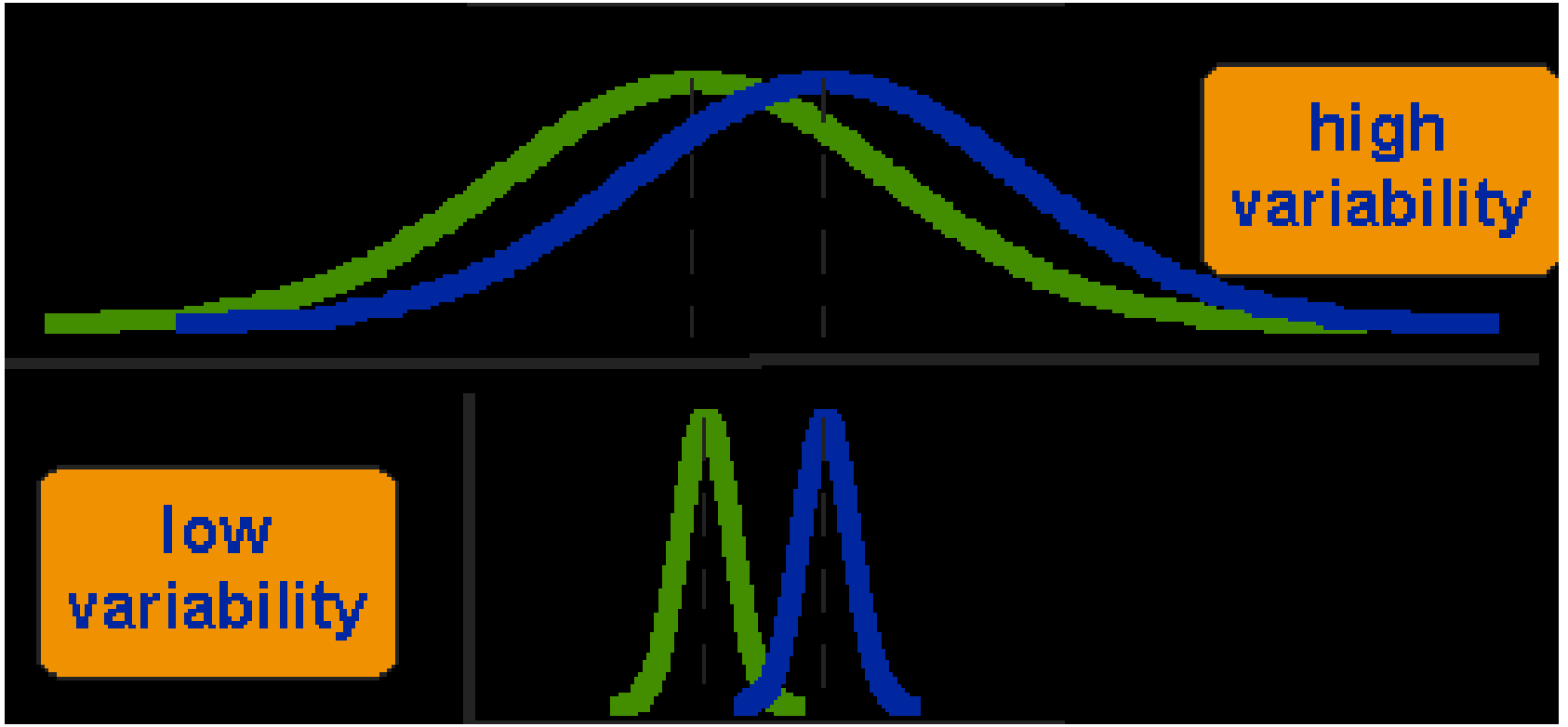
Notation

- Population values are denoted with Greek letters. The population means of Test (T) and reference (R) formulations are μ_T and μ_R
- The sample estimators of these parameters are random variables and are represented with capital letters such $\bar{Y}_T$, $\bar{Y}_R$, $\bar{Y}_D$, S_{WR}, SE_D. $\bar{Y}_T$, $\bar{Y}_R$ and S_{WR} are the sample estimators of μ_T, μ_R and s_{WR}, respectively. $\bar{Y}_D$ is the $\bar{Y}_T$- $\bar{Y}_R$ difference, and the standard error of this difference is SE_D. The true population value of SE_D is σ_D
- Realization of the random values (i.e. numbers) are $\bar{y}_T$, $\bar{y}_R$, $\bar{y}_D$, s_{WR} and se_D.
- θ – the regulatory constant (0.76 in the EU)

The types of equivalence -graphical interpretation of the concept



Relative difference or overlap

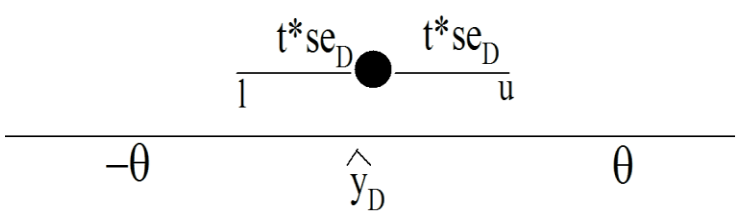
Difference between means

ABE, SABE, RSABE - definition and interpretation

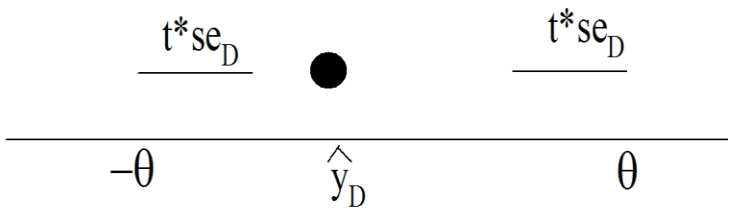
	Equivalence Test Hypothesis	Interpretation, comment
Average bioequivalence (ABE)	$-\theta \leq (\mu_T - \mu_R) \leq \theta$	Difference between means
Scaled Average Bioequivalence (SABE)	$-\theta \leq (\mu_T - \mu_R)/\sigma_W \leq \theta$	Standardized mean (β), overlap, effect size (Cohen's d)
Reference Scaled Average Bioequivalence (RSABE)	$-\theta \leq (\mu_T - \mu_R)/\sigma_{WR} \leq \theta$	Overlap relative to the reference, effect size (Glass' d)

Flavors of the ABE algorithm – The confidence interval based and the TOST variant

Confidence interval



TOST



1- Estimate the l and u interval limits
2- If they are in the $[-\theta,\theta]$ range then BE

H01: Test that $-\theta$ is equal or larger than the point estimate
H02: Test that θ is equal or smaller than the point estimate
If both tests reject H0 then BE.

Visually: the two tests also define a range where the point estimate should be.

RSABE algorithms: The ABEL method

- S_{WR} is treated as if it were a constant. Essentially, the ABEL approach traces the RSABE problem back to the well-established method evaluating ABE
- Rearranging the RSABE test criterion gives

1.	$l = \bar{y}_D - t(0.95,df)*se_D$	same as in ABE
2.	$u= \bar{y}_D + t(0.95,df)*se_D$	same as in ABE
3.	$s_{WR}\,\theta \le l < u \le s_{WR}\,\theta$	instead fixed θ we have random limit

Advantages and disadvantages of the ABEL method

- As the name suggests it is not a RSABE test but „Average Bioequivalence with Expanding Limit”
- Pro
  - Easy to calculate
  - Easy to interpret
  - Official in the EU, Australia, Canada.
- But the consumer error is higher than the nominal 5%
  - 7%-9%
  - This was always clear starting from Boddy et al.(1995)

RSABE algorithms: The Hyslop's method

- Hyslop et al., proposed for IBE (2000)
- We simplified it for RSABE (2003), currently recommended by the FDA
- The starting point is the rearranged and squared criterion
  - $(\mu_T - \mu_T)^2 - \theta^2 * \sigma_{WR}^2 \leq 0$
  - Background: Let W and Y two random variables. Their estimates $\hat{w}$ and $\hat{y}$. Let u_W and l_w of W, and u_y and l_y the estimated lower and upper confidence interval limits of W and Y. Howe showed that

$$l = \hat{w} - \hat{y} + \sqrt{(\hat{w} - l_W)^2 + (u_y - \hat{y})^2}$$

$$u = \hat{w} - \hat{y} + \sqrt{(u_W - \hat{w})^2 + (\hat{y} - l_y)^2}$$

Applying Howe's approximation we get the Hyslop's algorithm for RSABE

Hyslop's algorithm for RSABE

- Pro
  - Theoretically correct
  - FDA backed
- But
  - Cl has no meaning (what does it mean Cl =0.03?)
  - Requires programming- not that simple
  - Consistent but biased test (Tothfalusi and Endrenyi, AAPS ,2016)

1. $E_m = (\hat{y}_T - \hat{y}_R)^2$
2. $E_s = \theta^2 * s_{WR}^2$
3. $C_m = [Abs(\hat{y}_T - \hat{y}_R) + t * se_D]^2$
4. $C_s = \theta^2 * df\ s_{WR}^2/\chi^2$
5. $L_m = (C_m - E_m)^2$
6. $L_s = (C_s - E_s)^2$
7. $Cl = E_m - E_s + (L_m + L_s)^{½}$
8. Bioequivalent if $Cl < 0$.

Exact algorithms for RSABE

- Hyslop's algorithm is based on approximation
- Can we do without it ?

RSABE definition in terms of population parameters

Idea: $-\theta \le (\mu_T - \mu_R)/\sigma_{WR} \le \theta$

Working definition →

RSABE definition in terms of estimators (random variables)

$\text{Prob}(-\theta \le \bar{Y}_D / S_{WR} \le \theta) > 0.9$

Ratio of a normally ditributed and a χ^2 distributed random $vv - s$
Similar to noncentral t…

The distribution of $\bar{Y}_D / S_{WR}$

Assume that there is k constant that $\sigma_D = k^* \sigma_{WR}$

Substitute the definion of k

$$\bar{Y}_D \sim N(\mu_T - \mu_R, k * \sigma_{WR})$$

$$S_{WR} \sim \sigma_{WR} \sqrt{\chi^2/df}$$

$$\frac{\bar{Y}_D}{S_{WR}} \sim \frac{N(\mu_T - \mu_R, k)}{\sqrt{\chi^2/df}}$$

After divison simplify the right side with σ_{WR}

$$k^{-1} \frac{\bar{Y}_D}{S_{WR}} \sim \frac{N(\lambda,1)}{\sqrt{\chi^2/df}}$$

Multiply with k^{-1} both sides and define λ as = $k^{-1} (\mu_T - \mu_R)/\sigma_{WR}$.

Noncentral t by definition

So we showed that $k^{-1}\bar{Y}_D / S_{WR}$ is distributed as noncentral t with $\lambda = k^{-1}(\mu_T - \mu_R)/\sigma_{WR}$. But λ is unknown.

Idea: Construct an equivalence test for the $\lambda = k^{-1}(\mu_T - \mu_R)/\sigma_{WR}$ noncentrality parameter. If we know that λ is in $[-k^{-1}\theta, k^{-1}\theta]$ range with 90% confidence then also $k\lambda = (\mu_T - \mu_R)/\sigma_{WR}$ will be in the $[\theta, \theta]$ range.

$$\text{Prob}(-\theta \leq \bar{Y}_D / S_{WR} \leq \theta) \geq 0.9$$

They are equivalent

$$\text{Prob}(-k^{-1}\theta \leq k^{-1}\bar{Y}_D / S_{WR} \leq k^{-1}\theta) \geq 0.9$$

Seems that we have a test but actually we do not…. Hedges' correction.

The point is that ABEL and Hyslop tests are equivalence tests for the population mean (δ) of the $\bar{Y}_D / S_{WR}$ statistics. Hedges showed that the λ noncentrality parameter is not equal with the δ. The following relationship holds:

$\delta = H_f^{-1}\lambda$ where $H_f = 1 - 3/(4df-1)$ where df is the degree of freedom of S_{WR}.

For example if df = 6 then $\delta = 1.15\lambda$.

Idea: Multiply θ with H_f . A test for λ is also a test for δ.

$Conf(-H_f k^{-1}\theta \leq \lambda \leq H_f k^{-1}\theta) \geq 0.9$ —Multiply with H_f^{-1}→ $Conf(-k^{-1}\theta \leq \delta \leq k^{-1}\theta) \geq 0.9$

Only and only If this is true

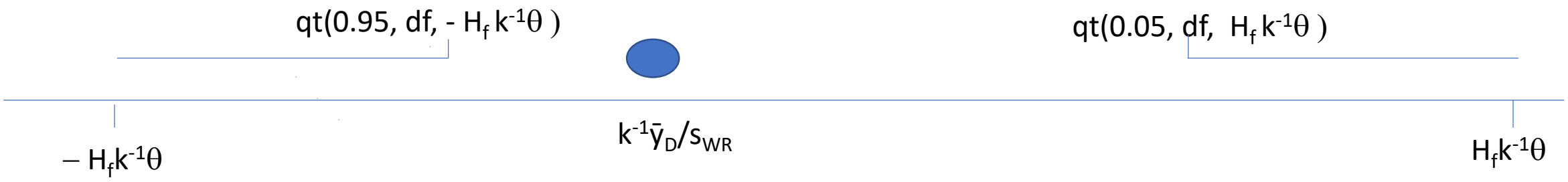
this will be also true

Conclusion: The RSABE test was derived back to an equivalence test for a noncentrality parameter (λ) of a noncentraly distributed t variable. If the original range was $[-\theta, \theta]$ then we should test that λ is in $[-H_f k^{-1}\theta, H_f k^{-1}\theta]$

What about „k”?

- The constant „k” is the ratio of the standard deviation of $\bar{Y}_D$ and σ_{WR}.
- If we assume that σ_{WR}= σ_{WT} then it depends only on the design. For example for the TRTR-RTRT design it is $n^{-0.5}$.
- Using contrast we can give formula even for the heteroscedastic case. But of course we can be never sure that σ_{WT}/ σ_{WR}= 1.
- We initially proposed (AAPS,2016) first estimate the σ_{WT}/ σ_{WR} ratio and using that to calculate k. This step was difficult and was practically impossible for partial replicate design (TRR-RTR-RRT).
- But we „rediscovered” paper of Schall (1995) who gave a very simple solution: k= se_D /s_{WR}--→ Just use the estimates of the output !

The RSABE problem: Given the point estimate $\bar{y}_D/s_{WR}$ make a statement that $E(\bar{Y}_D/S_{WR})$ is in the $[-\theta, \theta]$ range. The TOST solution. (The NcTOST algorithm)



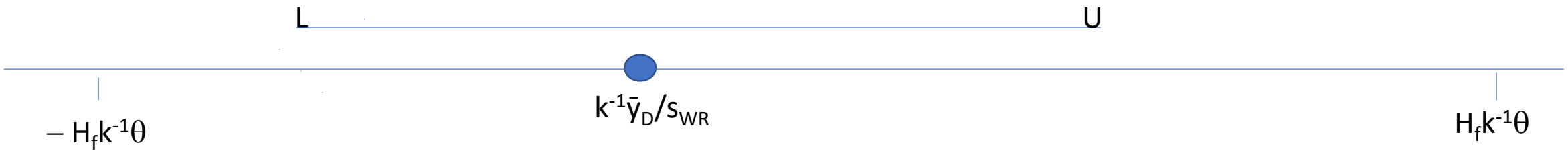
Step 1. Compute $k = se_D/s_{WR}$

Step 2. Compute L_θ = qt(0.95, df, - $H_f k^{-1}\theta$) and U_θ = qt(0.05, df, $H_f k^{-1}\theta$)

Step 3. If $L_q < k^{-1}\bar{y}_D/s_{WR} < U_q$ accept the RSABE hypothesis else reject

qt = Quantile function of a noncentral t variables (see R base documentation)

The RSABE problem: Given the point estimate $\bar{y}_D/s_{WR}$ make a statement that $E(\bar{Y}_D/S_{WR})$ is in the $[-\theta, \theta]$ range. The classical confidence interval solution. (The NcConf algorithm)



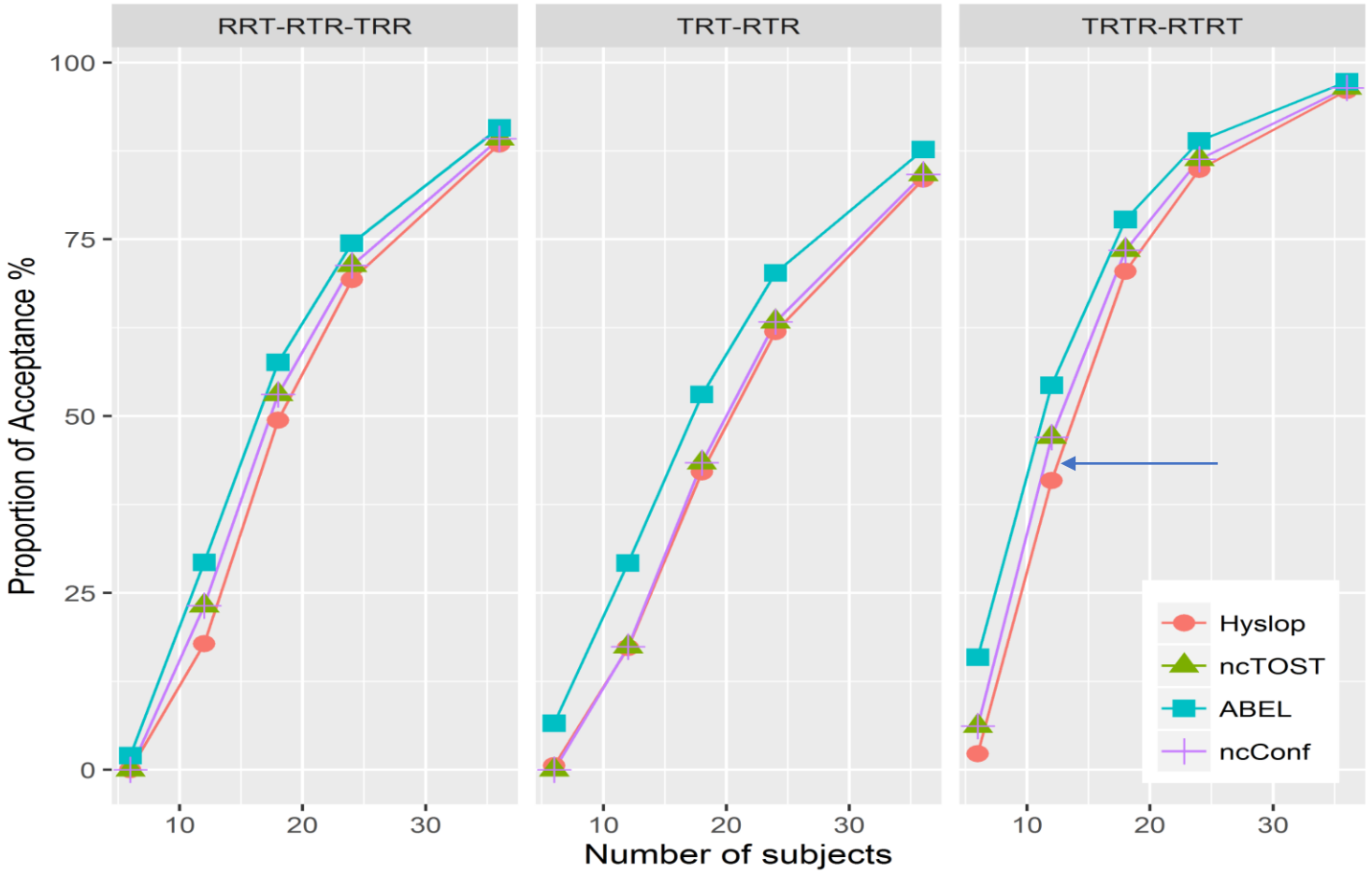
Step 1. Compute $k = se_D/s_{WR}$

Step 2. Estimate the lower (L) and upper (U) confidence limits for $k^{-1}(\mu_T - \mu_R)/\sigma_{WR}$ The calculation requires solving two nonlinear equations, solving $qt(0.95, df, L) = k^{-1}\bar{y}_D/s_{WR}$ and $qt(0.05, df, U) = k^{-1}\bar{y}_D/s_{WR}$ for L and U.

Step 3. RSABE is established if $L \geq -H_f k^{-1}\theta$ és $U \leq H_f k^{-1}\theta$.

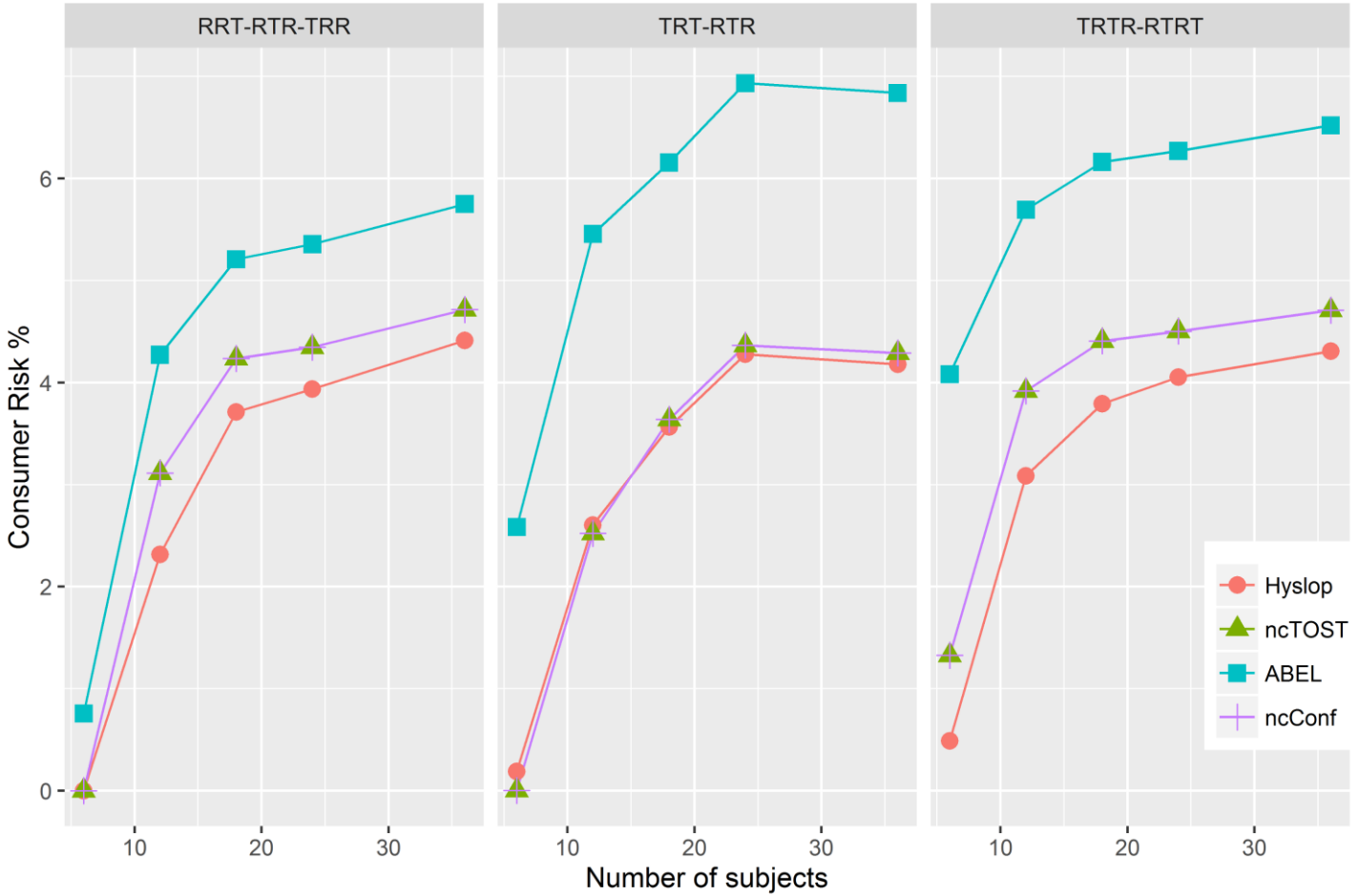
Step 4. (Optional) The confidence limits for $(\mu_T - \mu_R)/\sigma_{WR}$ are kL and kU.

Simulations: Power



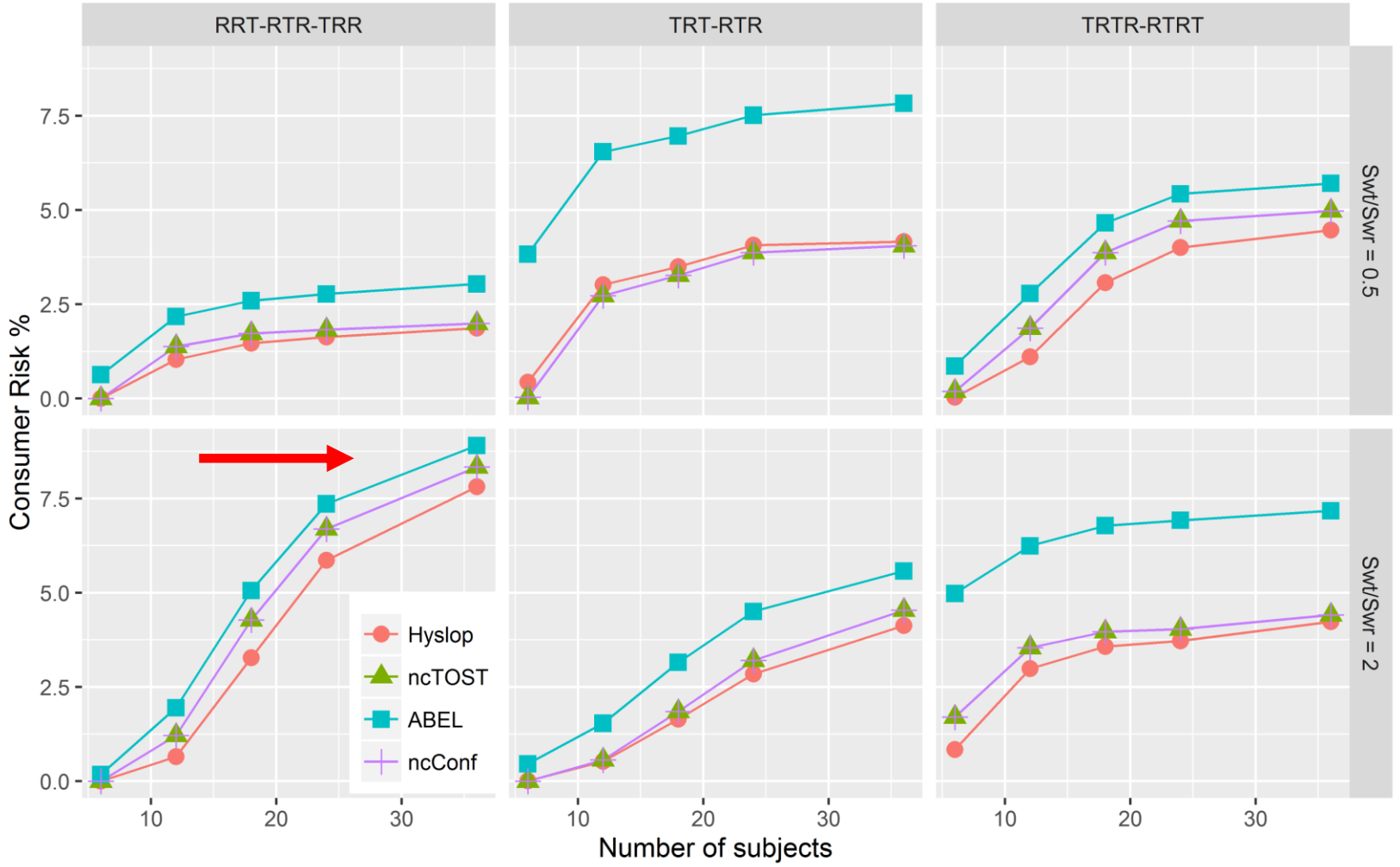
The approximate Hyslop method has noticeably lower power. For example, the acceptances were, with twelve subjects and the TRTR-RTRT design, 54.6, 47.1, 47.1 and 40.9 % with the ABEL, ncTOST, ncConf and Hyslop's algorithms

Simulations: Consumer Risk $\sigma_{WR} = \sigma_{WT}$



The consumer risk remains below 5 % with both variants of the Exact algorithms.

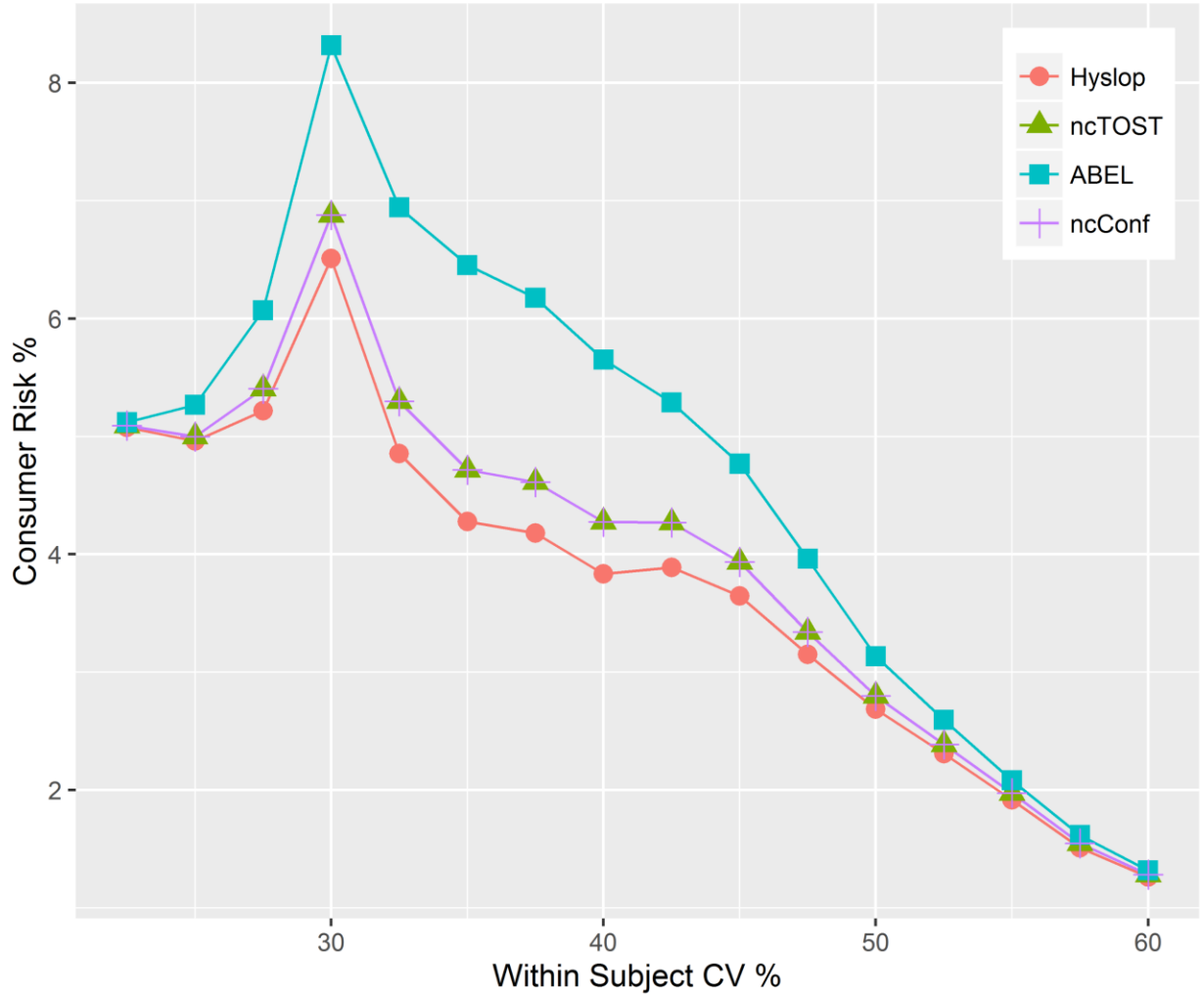
Simulated trials where σ_{WT}/σ_{WR} was either 0.5 (upper row) or 2 (lower row).



Observe that with partial replicate design and σ_{WT}/σ_{WR} = 2 condition („bad generic”) , the consumer risk increased steadily and significantly above the 5% limit with **each** algorithm.

Mixed strategy: The „Blip”

The consumer risk is above 5% with all algorithms but returns, around CV_{WR}=35%, below the nominal level with the Hyslop and Exact algorithms. The same pattern can be observed with ABEL except that it remains above the 5% level



Conclusions

- The NcTOST algorithm is a one-liner, can be computed without programing. Compared to the Hyslop's approximation, at small sample size it is more powerful (not biased).
- The NcConf is computationally more complex but it provides exact confidence intervals.
- The consumer risk with the Hyslop's and Exact algorithms are below 5% except in two cases: partial replicate design and around CV_{WR}= 30%.
- Paradoxically the partial replicate design is the recommended design by the EMA.
- The difference between $E(\bar{Y}_D / S_{WR})$ and $(\mu_T-\mu_R)/\sigma_{WR}$ raises new questions.
- Biosimilarity implications:
  - BE studies (including the PD part)
  - Comparative assessment of quality attributes?

History

- Schall provided the first version of the Exact algorithm. (1995)
- The version presented is based on Tothfalusi and Endrenyi (2017). It is an improved version compared to Tothfalusi and Endrenyi (2016).

References

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European Medicines Agency. Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP). 19 November 2015 EMA/618604/2008 Rev. 13, Question 19

Questions ?