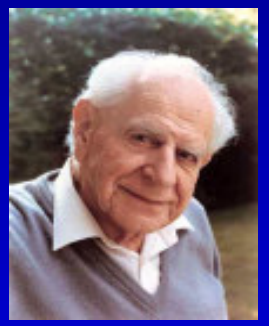
¡Bienvenidos!

Two-Stage Sequential Designs in Bioequivalence

Helmut Schütz
BEBAC

To bear in Remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.

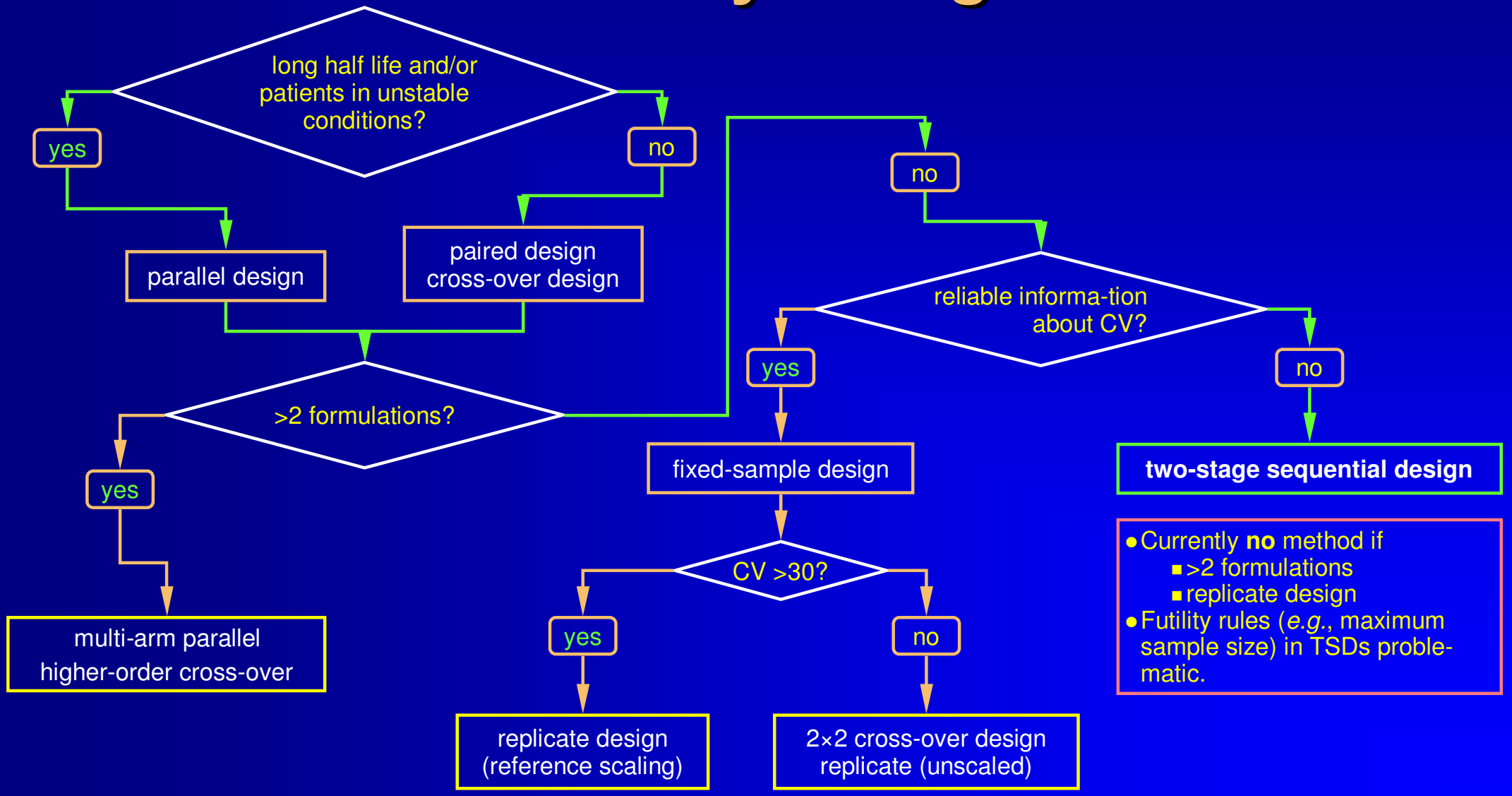


Karl R. Popper

Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

BE Study Designs



Add-on / Two-Stage Designs

- Sometimes properly designed studies fail due to
  - 'true' bioinequivalence,
  - pure chance (producer's risk),
  - poor study conduct (increasing variability),
  - false (mainly over-optimistic) assumptions about the *CV* and/or *T*/*R*-ratio – leading to a too small sample size (insufficient power).
- The sample size is planned based on *assumptions*…

Add-on / Two-Stage Designs

- Dealing with *inconclusive* BE studies (confidence interval not entirely with the acceptance range)
  - Repeat the study in a larger sample size.
  - Optionally perform a meta-analysis of pooled data. Only acceptable if at least one study demonstrates BE.
  - Recruit a second group of subjects and pool data?
- Discussed at Bio-International Conferences (1989, 1992) and guidelines from the 1990s.
  - The patient's risk must be preserved!
  - Among rivaling methods the one with with the highest power should be selected.

Terminology

- Add-On Designs
  - Sample sizes of both groups have a lower limit.
- Group Sequential Designs
  - Sample sizes of both groups are pre-specified.
- Adaptive Two-Stage Sequential Designs
  - Groups sizes are (generally) not limited.
  - Sample size of the second group is re-estimated from the first group's data.

H Schütz
Two-stage designs in bioequivalence trials
Eur J Clin Pharmacol (2015)
DOI: 10.1007/s00228-015-1806-2

Definition

- For an overview see Schwartz & Denne, Dragalin, Chow & Chang, and Chin
  - A study design is called *adaptive* if statistical methodology allows modification of a design element (*e.g.*, the sample size) at an interim analysis with full control of the type I error (TIE).

Schwartz TA and JS Denne JS (2003) *Common threads between sample size recalculation and group sequential procedures* Pharm Stat 2, 263–271. DOI: 10.1002/pst.068

Dragalin V (2006) *Adaptive Designs: Terminology and Classification* Drug Info J 40, 425–435

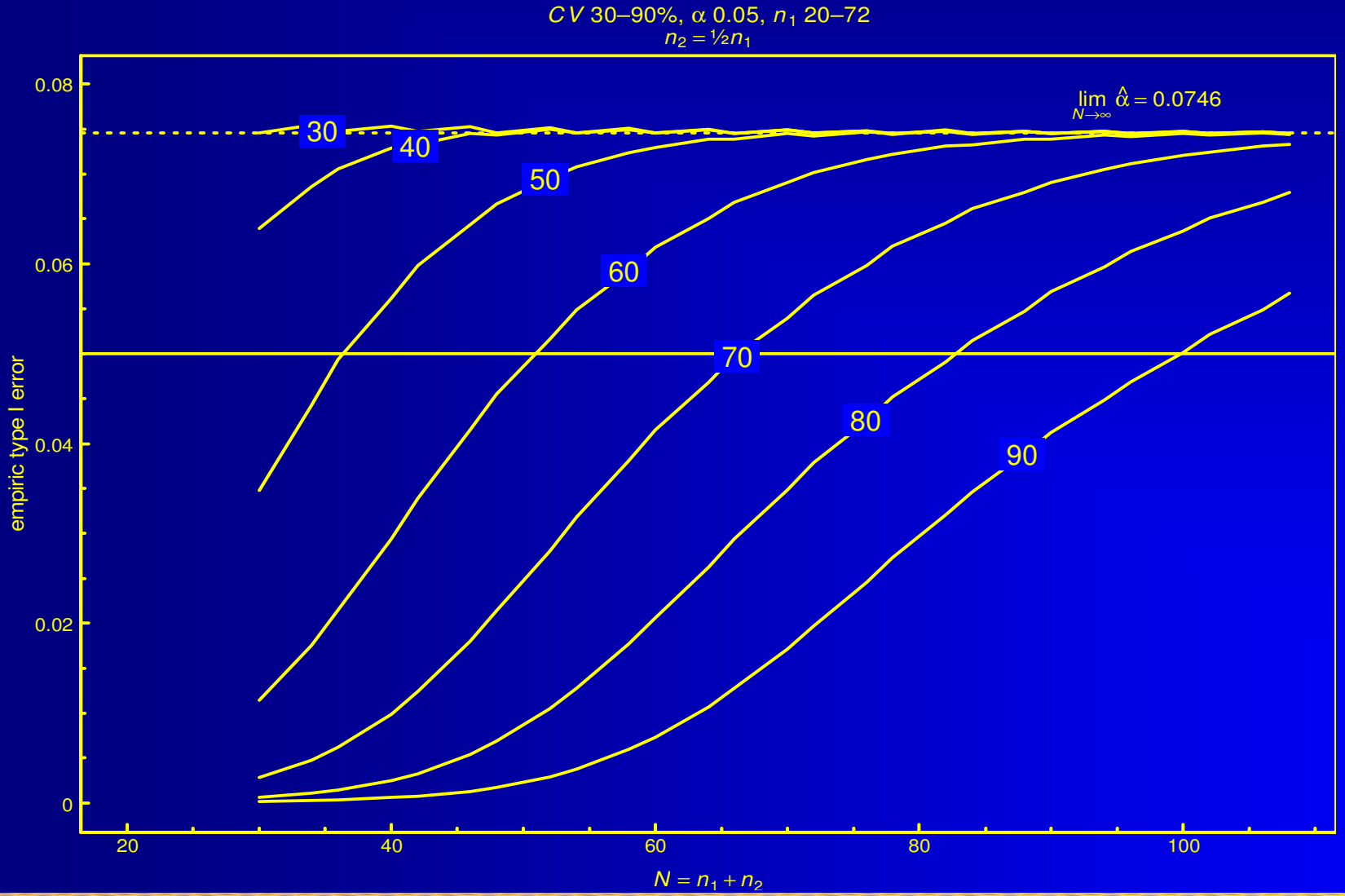
Chow S-C and M Chang (2012) *Adaptive Design Methods in Clinical Trials* 2nd edn. Chapman & Hall/CRC, Boca Raton

Chin R (2012) *Adaptive and Flexible Clinical Trials* Chapman & Hall/CRC, Boca Raton

Add-On Designs: Guidelines

- General conditions
  - Intention to perform an AOD has to be stated in the protocol,
  - the same batches of products, and
  - the same clinical and bioanalytical methods have to be employed in both groups.
- Currently only stated in GLs of Japan, Argentina, Mexico, and Korea
  - The patient's risk might be seriously compromised!

Add-on / Two-Stage Designs



Japan (2012)

- 1st group (n_1) ≥20 evaluated with α 0.05 (90% CI)
- 2nd group (n_2) ≥½n_1
- Pooled data evaluated with α 0.05 (90% CI)
- Inflation of the patient's risk (up to 7.5%)!

Wonnemann M, Frömke C, and A Koch (2015)
Inflation of the Type I Error: Investigations on Regulatory Recommendations for Bioequiva-lence of Highly Variable Drugs Pharm Res 32(1), 135–43
DOI: 10.1007/s11095-014-1450-z

Group Sequential Designs

- Long and accepted tradition in clinical research (mainly phase III)
  - Based on work by Armitage *et al.* (1969), McPherson (1974), Pocock (1977), O'Brien and Fleming (1979), Lan and DeMets (1983), …
    - Developed for superiority testing, normal distributed data with known variance, fixed and equal sizes of groups.
    - First proposal by Gould (1995) in the field of BE did not get regulatory acceptance in Europe.

AL Gould
Group Sequential Extension of a Standard Bioequivalence Testing Procedure
J Pharmacokin Biopharm 23(1), 57–86 (1995)
DOI: 10.1007/BF02353786

Group Sequential Designs: GLs

- Australia (2004), Canada (Draft 2009)
  - Application of Bonferroni's correction (α 0.025).
  - Theoretical TIE $\leq$0.0494.
  - For *CVs* and samples sizes typical in BE $\leq$0.04.
- Canada (2012)
  - Pocock's α 0.0294.
  - n_1 based on 'most likely variance' + additional subjects to compensate for expected dropout-rate.
  - Total sample size based on 'worst-case scenario'.
  - If $n_2 \neq n_1$ relevant inflation of the TIE is possible!

Adaptive TS Sequential Designs

- Methods by Potvin *et al.* (2008) first validated framework in the context of BE
  - Supported by the '**P**roduct **Q**uality **R**esearch **I**nstitute' (members: FDA/CDER, Health Canada, USP, AAPS, PhRMA…).
  - Inspired by conventional BE testing and Pocock's α 0.0294 for Group Sequential Designs.

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, and RA Smith
Sequential design approaches for bioequivalence studies with crossover designs
Pharm Stat 7(4), 245–62 (2008) DOI: 10.1002/pst.294

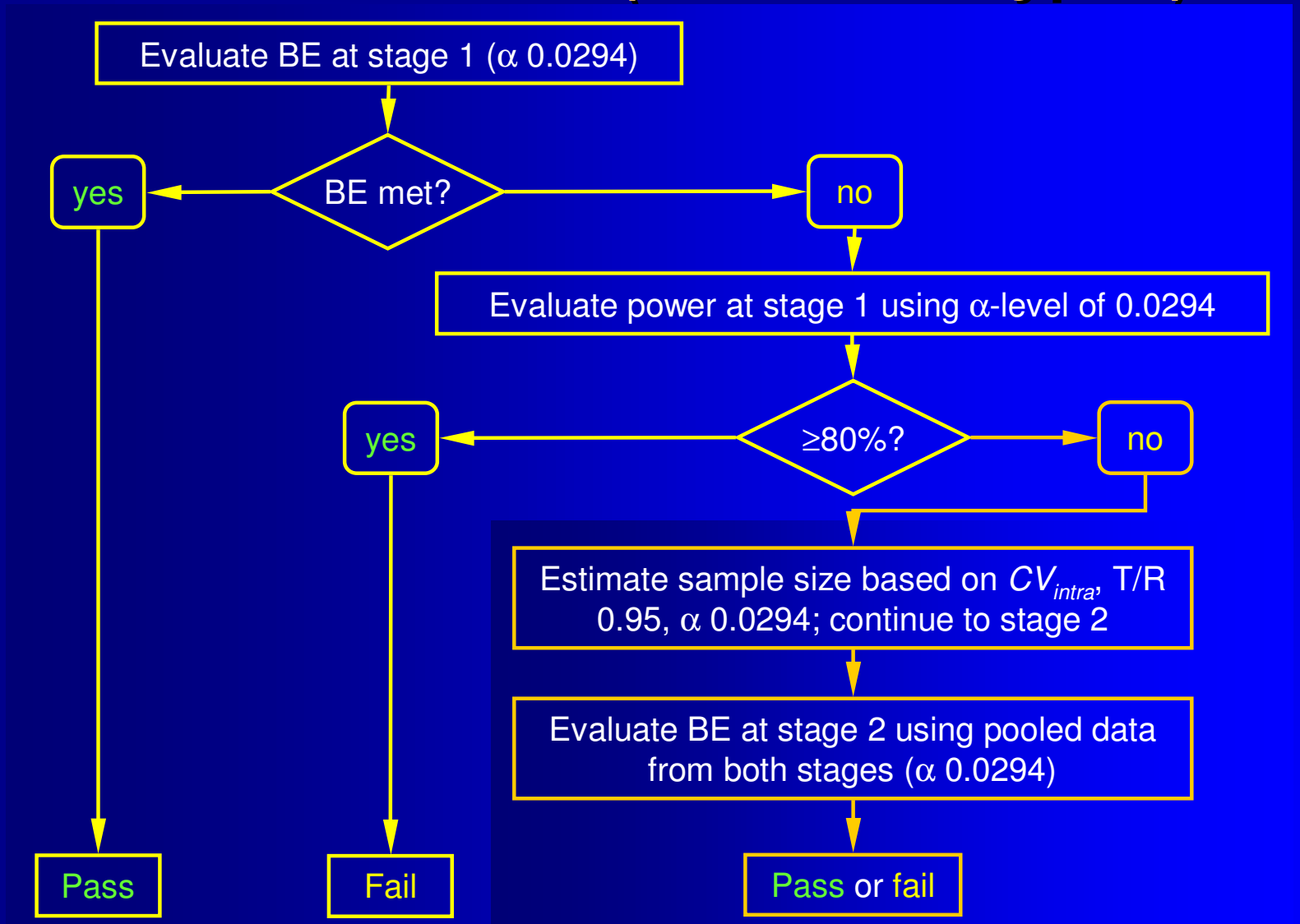
Adaptive TS Sequential Designs

- Two ‘types’ of TS Sequential Designs
  1. The *same* adjusted α is applied in both stages (regardless whether a study stops already in the first stage or proceeds to the second stage).
     - Based on Group Sequential Design.
     - In publications called Method B.
  2. An unadjusted α *may* be used in the first stage (dependent on interim power).
     - Based on conventional BE testing + GSD.
     - In publications called Method C, D, C/D.

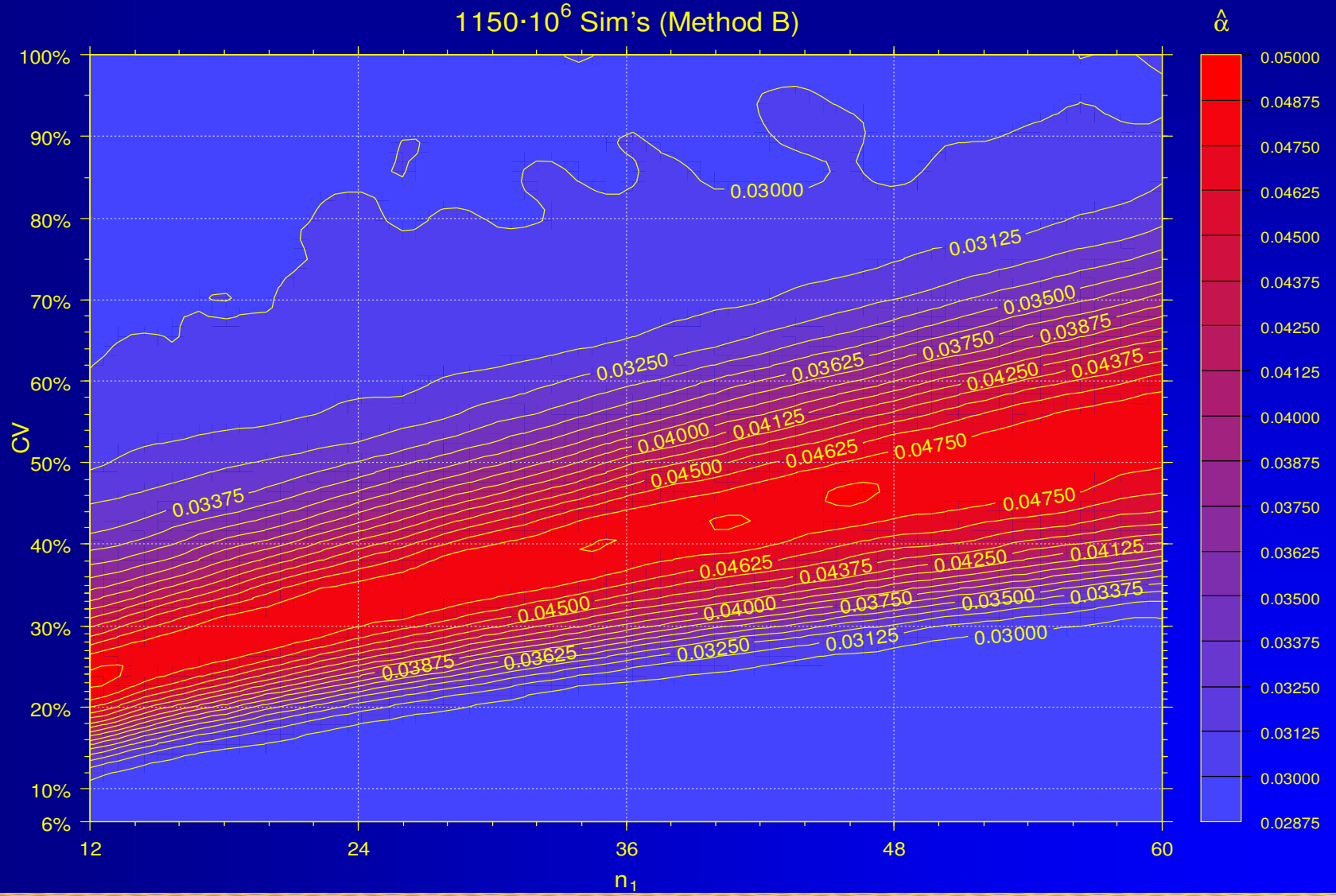
Review of Guidelines

- **EMA (Jan 2010)**
  - Acceptable; Potvin *et al.* Method B preferred (?)
- **Canada (May 2012)**
  - Potvin *et al.* Method C recommended.
- **FDA (Jun 2012)**
  - Potvin *et al.* Method C/D recommended.
  - API specific guidance: Loteprednol
- **Russia (2013)**
  - Acceptable; Potvin *et al.* Method B preferred (?)

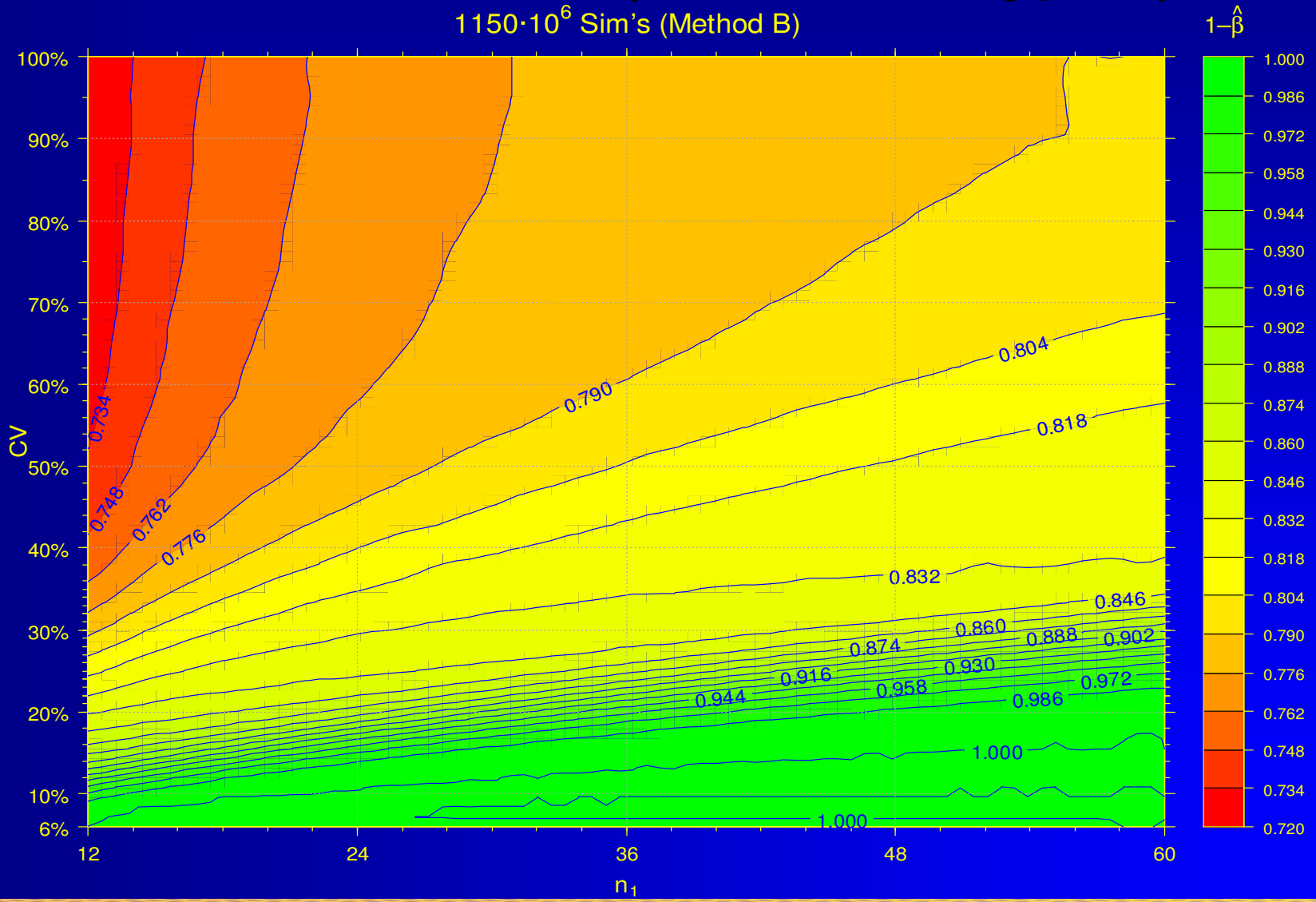
Potvin *et al.* (Method B – type 1)



Potvin *et al.* (Method B – type 1)



Potvin *et al.* (Method B – type 1)



Potvin *et al.* (Method B – type 1)

- Technical Aspects
  - Only *one* Interim Analysis (after stage 1).
  - Potvin *et al.* used a simple power estimation based on the shifted central *t*-distribution. Use software (avoid approxi-mations). Example 2:

method	% power
approx. (shifted central *t*)	50.49
approx. (noncentral *t*)	52.16
exact (Owen's *Q*)	52.51

  - Should be termed 'Interim Power Analysis' – *not* 'Bioequivalence Assessment' in the protocol.
  - No *post hoc* Power – only a validated method to guide the decision tree.
  - No adjustment for *T*/*R*-ratio observed in stage 1!

Potvin *et al.* (Method B – type 1)

- Technical Aspects (cont'd)
  - No futility rule preventing to go into stage 2 with a high sample size!
    Must be clearly stated in the protocol (unfamiliar to the IEC because common in Group Sequential Designs).
  - Pocock's α 0.0294 is used in stage 1 and in the pooled analysis (data from stages 1 + 2),
    i.e., the $100(1 - 2\times\alpha) = 94.12\%$ CI is calculated.
  - Overall TIE preserved at ≤ 0.05.

Potvin *et al.* (Method B – type 1)

- Technical Aspects (cont'd) + EMA modification
  - If the study is stopped after stage 1, the statistical model is:

```
fixed:  sequence + period + treatment
+ subject(sequence)
```

  - If the study continues to stage 2, the model for the combined analysis is:

```
fixed:  stage + sequence + sequence(stage)
        + subject(sequence × stage) + period(stage)
        + treatment
```

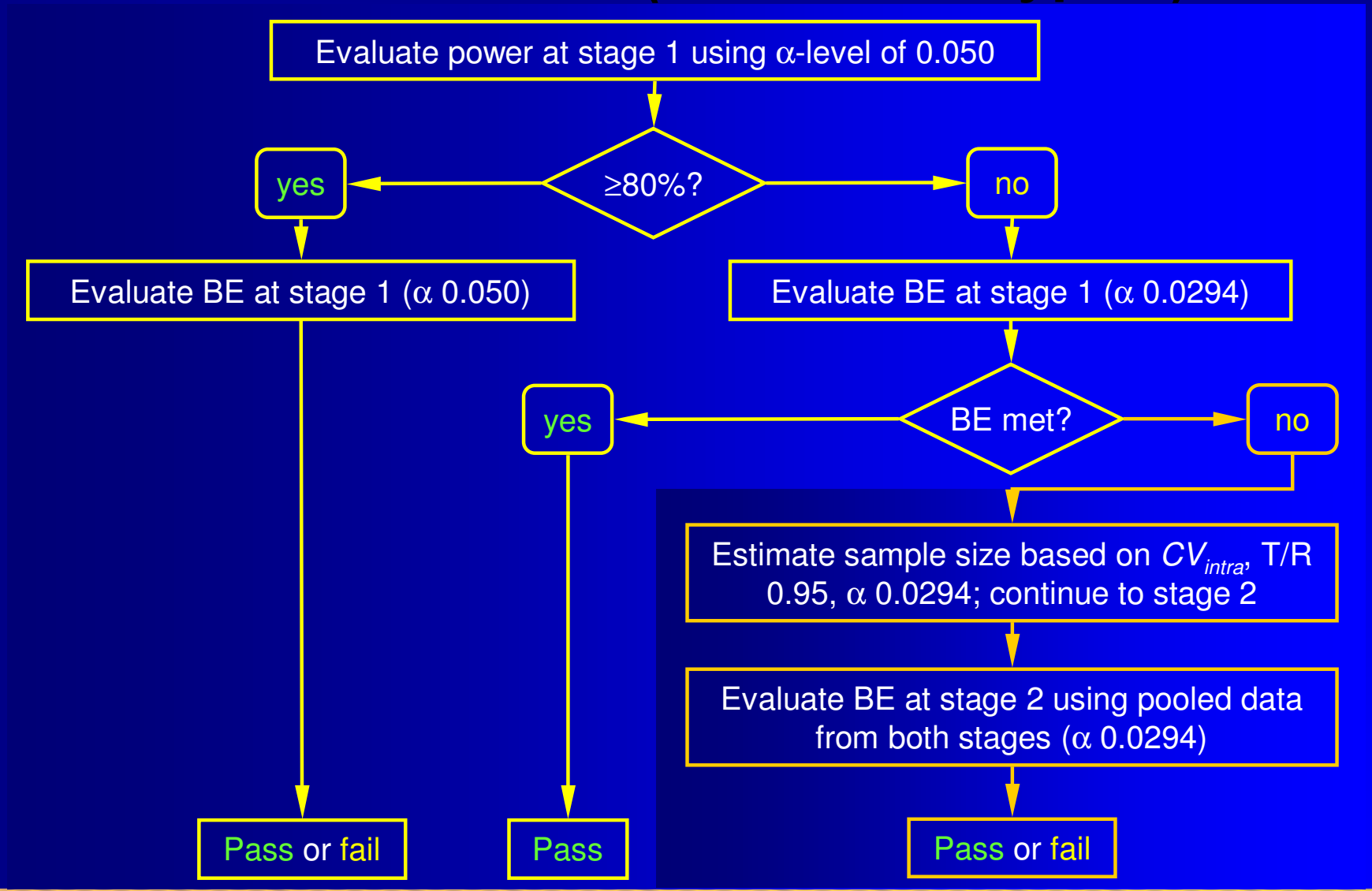
  - No poolability criterion! Combining is *always allowed* – even if a significant difference between stages is observed. No need to test this effect.

Potvin *et al.* (Method B – type 1)

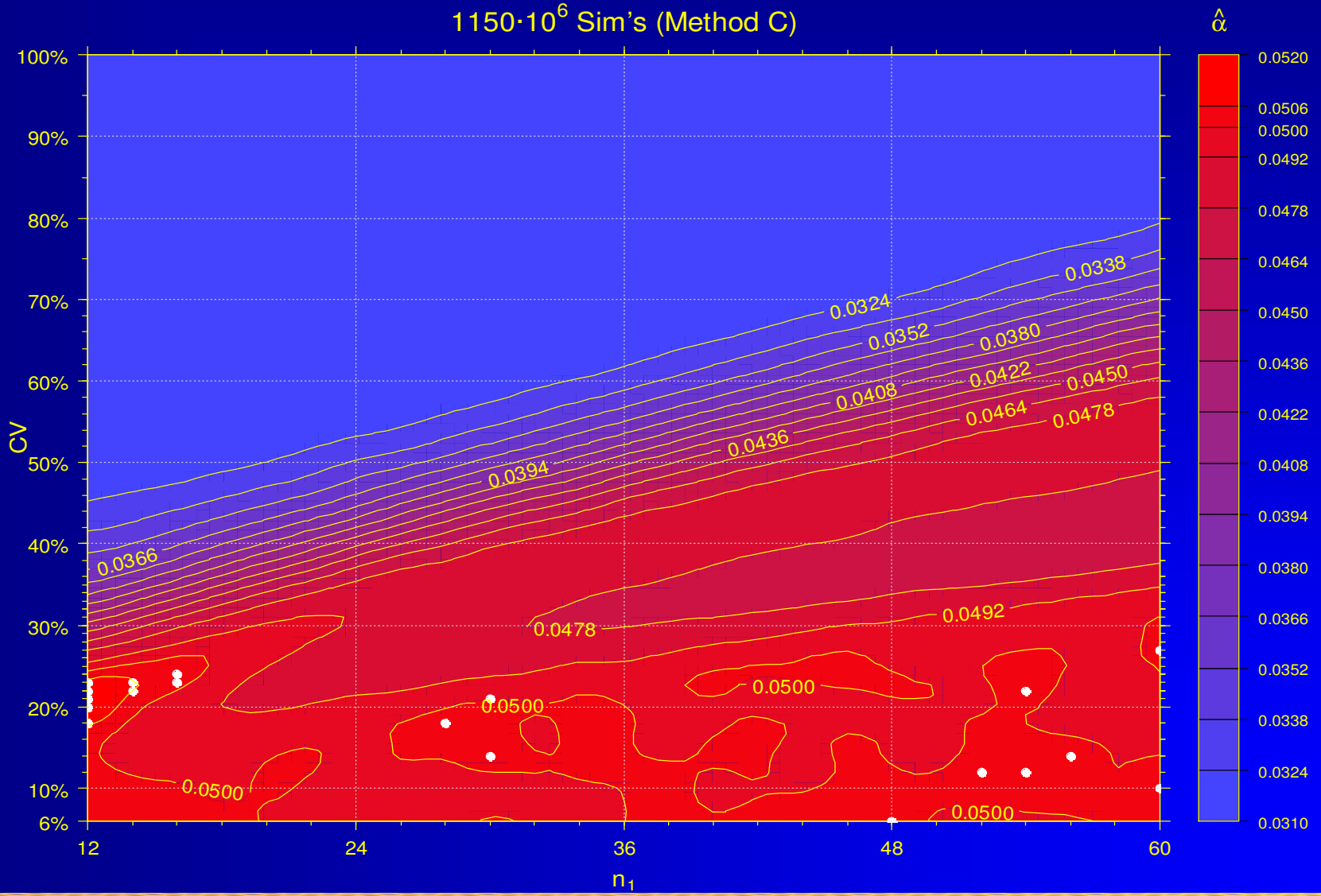
- Technical Aspects (cont'd) + EMA modification
  - Incomprehensible why this modification was introducted by EMA's Biostatistical Working Party
    - Simulations performed or "gut feeling"?
      - Modification shown to be irrelevant.
      - Furthermore no difference whether subjects were treated as a fixed or random term (*unless* T/R >1.20).

Karalis V and P Macheras
On the Statistical Model of the Two-Stage Designs in Bioequivalence Assessment
J Pharm Pharmacol 66(1), 48–52 (2014) DOI: 10.1111/jphp.12164

Potvin *et al.* (Method C – type 2)



Potvin *et al.* (Method C – type 2)



Potvin *et al.* (Method B/C – type 1/2)

- Pros & Cons
  - Method C (*if power* ≥*80%*) is a conventional BE study; no penalty in terms of α needs to be applied.
  - Method C proceeds to stage 2 less often and has smaller average total sample sizes than Method B for cases where the initial sample size is reasonable for the *CV*.
  - If the size of stage 1 is low for the actual *CV* both methods proceed to stage 2 almost all the time; total sample sizes are similar.
  - Method B slightly more conservative than C.

Type 1/2

- Recommendations
  - Type 2 preferred due to slightly higher power than type 1 (FDA, HPFB). Type 1 for EMA (?)
  - Plan the study *as if* the *CV* is known
    - If assumptions turn out to be true = no penalty
    - If lower power (*CV* higher than expected), BE still possible in first stage (penalty; 94.12% CI) or continue to stage 2 as a 'safety net'.
  - Don't jeopardize! Small sample sizes in the first stage don't pay off. Total sample sizes are ~10–20% higher.

TSDs: Alternatives

- Methods by Potvin *et al.* (2008) limited to *T*/*R* of 0.95 and 80% power
  - Follow-up publications (*T*/*R* 0.95…0.90, 80…90% power)

reference	type	method	*T*/*R*	target power	*CV*	α_{adj}	max. TIE
Potvin *et al.*	1	B	0.95	80%	10–100%	0.0294	0.0485
	2	C					0.0510
Montague *et al.*	2	D	0.90			0.0280	0.0518
Fuglsang	1	B	0.95	90%	10–80%	0.0284	0.0501
	2	C/D				0.0274	0.0503
	2	C/D	0.90			0.0269	0.0501

Montague TH, Potvin D, DiLiberti CE, Hauck WW, Parr AF, and DJ Schuirmann
Additional results for 'Sequential design approaches for bioequivalence studies with crossover designs'
Pharm Stat 11(1), 8–13 (2011) DOI: 10.1002/pst.483
A Fuglsang
Sequential Bioequivalence Trial Designs with Increased Power and Controlled Type I Error Rates
AAPS J 15(3), 659–61 (2013) DOI: 10.1208/s12248-013-9475-5

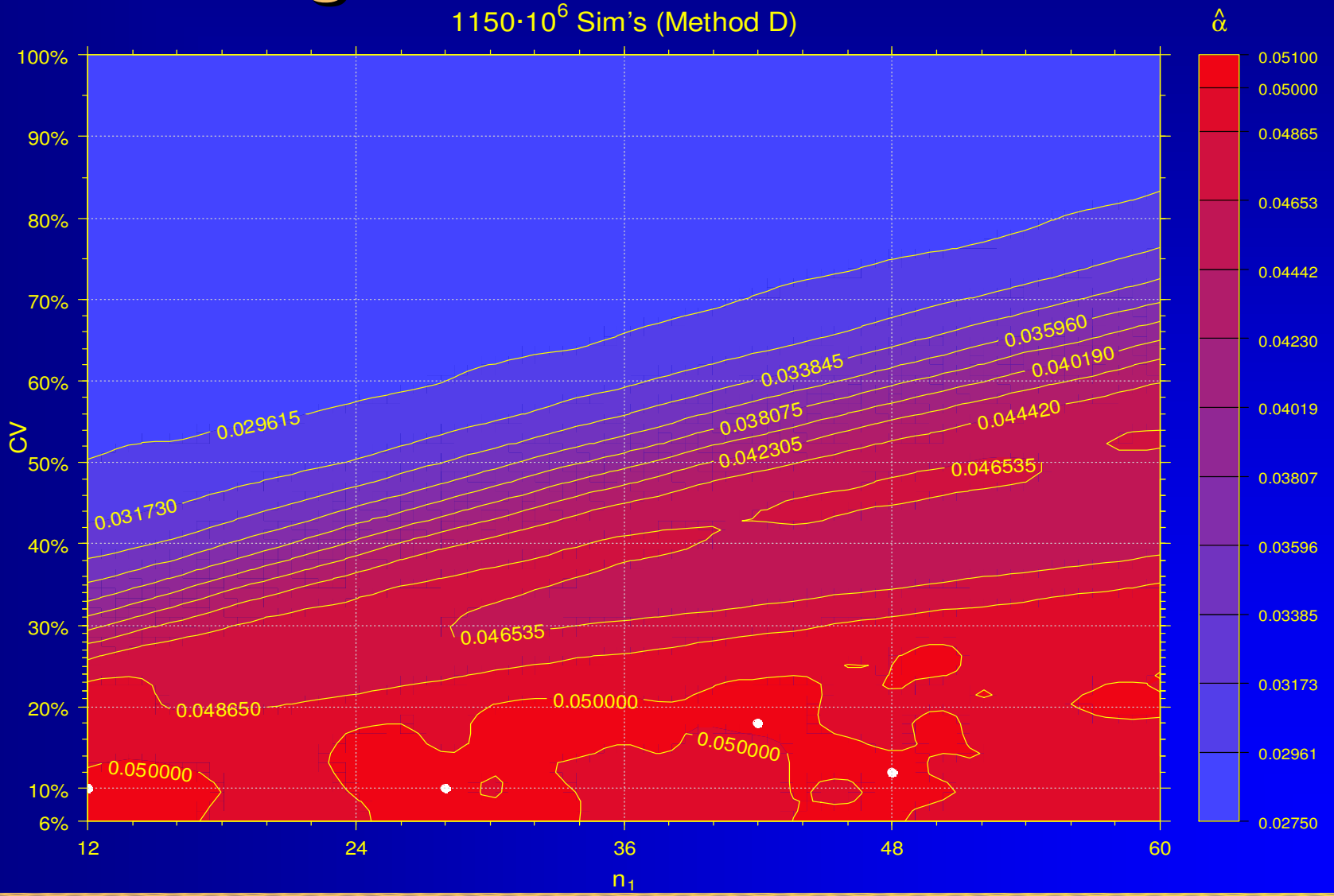
TSDs: Alternatives

- Slight inflation of the TIE in some 'type 2' designs could easily be avoided
  - Modifications of published adjusted α

type	method	*T/R*	α_{adj}	max. TIE	α_{adj}*	max. TIE*
1	B	0.95	0.0294	0.0485	0.0304	0.0501
2	C			0.0510	0.0282	0.0500
2	D	0.90	0.0280	0.0518	0.0270	0.0500

* Schütz H, Labes D, and A Fuglsang
Modifications of 'Sequential design approaches for bioequivalence studies with crossover designs'
in preparation (2015)

Montague *et al.* (Method D – type 2)



Parallel Groups (Type 1/2)

- Fuglsang (2014)
  - Based on Potvin's Methods B/C (α_{adj} 0.0294, 80% power)
  - Framework: n_1 48–120, *CV* 10–100%
    - equal allocation ($N_{Test} = N_{Reference}$)
    - equal and unequal variances of groups
    - conventional *t*-test and Welch-Satterthwaite approximation
  - Results
    - No significant inflation of the TIE
    - Power ≥78.4%

A Fuglsang
Sequential Bioequivalence Approaches for Parallel Designs
AAPS J 16(3), 373–8 (2014), DOI: 10.1208/s12248-014-9571-1

Futility Rules revised

- **EMA GL Section 4.1.8 'Two-stage design'**
  "[…] the stopping criteria should be clearly defined prior to the study."
  - **What does that mean?**
    - **Failing in stage 1 or the pooled analysis according to the chosen method.**
      → Part of the validated frameworks.
    - **Early stopping for futility (*e.g.*, 'bad' ratio, extreme stage 2 sample size caused by high *CV* – better to opt for reference-scaling…).**
      → Not validated. A misunderstanding by regulators (stopping criterion ≠ futility rule).

Futility Rules revised

- Introduction of a futility rule *does not* inflate the TIE, but power may drop substantially!
  - State stopping criteria unambiguously in the protocol.
  - If you want to introduce a futility rule, simulations are mandatory in order to maintain sufficient power.

    "Introduction of […] futility rules may severely impact power in trials with sequential designs and under some circumstances such trials might be unethical."

A Fuglsang
Futility Rules in Bioequivalence Trials with Sequential Designs
APPS J 16(19), 79–82 (2014) DOI: 10.1208/s12248-013-9540-0

Validation of Frameworks

- Jones and Kenward concluded that

  "[…] before using any of the methods […], their operating characteristics should be evaluated for a range of values of n_1, CV and true ratio of means that are of interest, in order to decide if the Type I error rate is controlled, the power is adequate and the potential maximum total sample size is not too great."

- Uncomplicated with current software
  - Automatically finding a suitable α_{adj} and validating for TIE and power takes ~20 minutes.

Jones B and MG Kenward
Design and Analysis of Cross-Over Trials
Chapman & Hall/CRC, Boca Raton (3rd ed. 2014)
D Labes
Package 'Power2Stage', Version 0.2-2 (2014-12-08)

Cost Analysis

- Consider certain questions:
  - Is it possible to assume a best/worst-case scenario?
  - How large should the size of the first stage be?
  - How large is the expected sample size in the second stage?
  - Which power can one expect in both stages?
  - Will intruction of a futility criterion substantially decrease power?
  - Is there a sample size penalty compared to a fixed-sample design?

Cost Analysis

- Example
  - Expected *CV* 20%, desired power is 80% for a *T*/*R*-ratio of 0.95. Comparison of a type 1 TSD with a conventional fixed-sample design (*n* 20, 83.5% power).

n_1	*E*[*N*]	Studies stopped in stage 1 (%)	Studies failed in stage 1 (%)	Power in stage 1 (%)	Studies in stage 2 (%)	Final power (%)	Costs (%)
12	20.6	43.6	2.3	41.3	56.4	84.2	+2.9
14	20.0	55.6	3.0	52.4	44.5	85.0	+0.2
16	20.1	65.9	3.9	61.9	34.1	85.2	+0.3
18	20.6	74.3	5.0	69.3	25.7	85.5	+3.1
20	21.7	81.2	6.3	74.9	18.8	86.2	+8.4
22	23.0	87.2	7.3	79.8	12.8	87.0	+15.0
24	24.6	91.5	7.9	83.6	8.5	88.0	+22.9

Cost Analysis

- Example (cont'd)
  - With 14 or 16 subjects in the first stage similar costs (*E*[*N*] ~20) are expected; with 16 one has a 66% chance to stop the study already in the first stage (62% chance to pass and 4% to fail).
  - With n_1 equal to the fixed design's *n* costs are expected to be 8% higher but we have a 75% chance to pass in the first stage and 86% power overall.
  - Power of the TSD is always larger than the one of the fixed-sample design – regardless the initial sample size and even if the assumed *CV* turns out to be correct.

Cost Analysis

- Example (cont'd)
  - If in a fixed-sample design the *CV* turns out to be higher than the assumed one, power will decrease, whereas in a TSD power is maintained.
  - Don't start the first stage always in a small group and *hope* for a *smaller than expected CV* – which would be substan-tially more economic than a fixed-sample design. This is not necessarily a good idea: With 12 subjects power in the first stage is only 41% and 56% of studies will proceed to the second stage.

Advanced Example

- ‘Must pass’ BE in stage 1 (first to file)
  - Fixed *T*/*R* 90% (pessimistic; very likely better).
  - Expected *CV* 20% (pilot study with two references).
  - Expected dropout rate ~30%; start with 88 to have $n_1 \geq 60$.
  - Targets
    - >90% power for n_1 60 – even for extreme *CV* of 45%.
    - 90% power for $n_1 \geq 60$ (*CV* 20%) in stage 1.
    - Not <80% power for *CV* ≥25% in stage 1.
    - Low probability to proceed to stage 2.

Advanced Example

- ‘Must pass’ BE in stage 1 (first to file)
  - Sponsor prefered Method B (EU submission…).
  - Fuglsang published α_{adj} 0.0269 for *T*/*R* 0.90 and 90% power – but only for Method C…
  - Same α_{adj} applicable for Method B?
  - Likely…
    - Potvin *et al.* showed less inflation of the TIE with Method B.
    - Fuglsang needed less adjustment in Method B.
    - But we have to justify that!
  - 10^6 simulations for the TIE and 10^5 for power.

Advanced Example

- ‘Must pass’ BE in stage 1 (first to file)
  - Targets met
    - 93% power for n_1 60 (*CV* 20%) and 90% for extreme *CV* of 45%.
    - 90% power for n_1 ≥60 (*CV* 20%) in stage 1.
    - Low chances to proceed to stage 2 with *CV* 20%:
      n_1 60: 6%, n_1 72: 1%
    - ≥80% power for *CV* ≥20% – even for a more extreme dropout rate.
    - $\alpha_{adj.}$ 0.0271 would work as well (with 0.0278 <0.052).
  - Study passed in the first stage (February 2014)

Case Study 1

- Method C: Study passed BE in stage 1 (49 subjects, *CV* 30.65%, 90% CI)
  - UK/Ireland: Unadjusted α in stage 1 not acceptable.
- Study passed BE with 94.12% CI as well (*post hoc* switch to Method B).
  - Austria: The Applicant should demonstrate that the type I error inflation, which can be expected from the chosen approach, did not impact on the decision of bioequivalence.
    - One million simulations based on the study's sample size and *CV*. TIE 0.0494 (95% CI: 0.0490 – 0.0498)

Case Study 2

- Method C: Study stopped in stage 1
  AUC power >80%: passed BE with 90% CI
  C_{max} power <80%: passed BE with 94.12% CI
  - The Netherlands: Adapting the confidence intervals based upon power is not acceptable and also not in accordance with the EMA guideline. Confidence intervals should be selected *a priori*, without evaluation of the power. Therefore, the applicant should submit the 94.12% confidence intervals for AUC.
    - AUC failed BE with 94.12% CI.
    - Sponsor repeated the study with a very (!) large sample size and failed on C_{max}. Project cancelled.

Case Study 3

- Method C: Two studies passed in stage 1
  (SD n=15, MD n=16; C_{max} *CV* 17.9%, 8.54%; 90% CIs)
- Would have passed with Method B as well; however, 94.12% CIs were *not* reported.
  - RMS Germany. Accepted by CMSs Austria, Denmark, Sweden, and The Netherlands.
  - Spain: Statistical analysis should be GLM. Please justify.
    - Evaluated with fixed-effects model.
      Both studies passed.
      Issue resolved (September 2013)

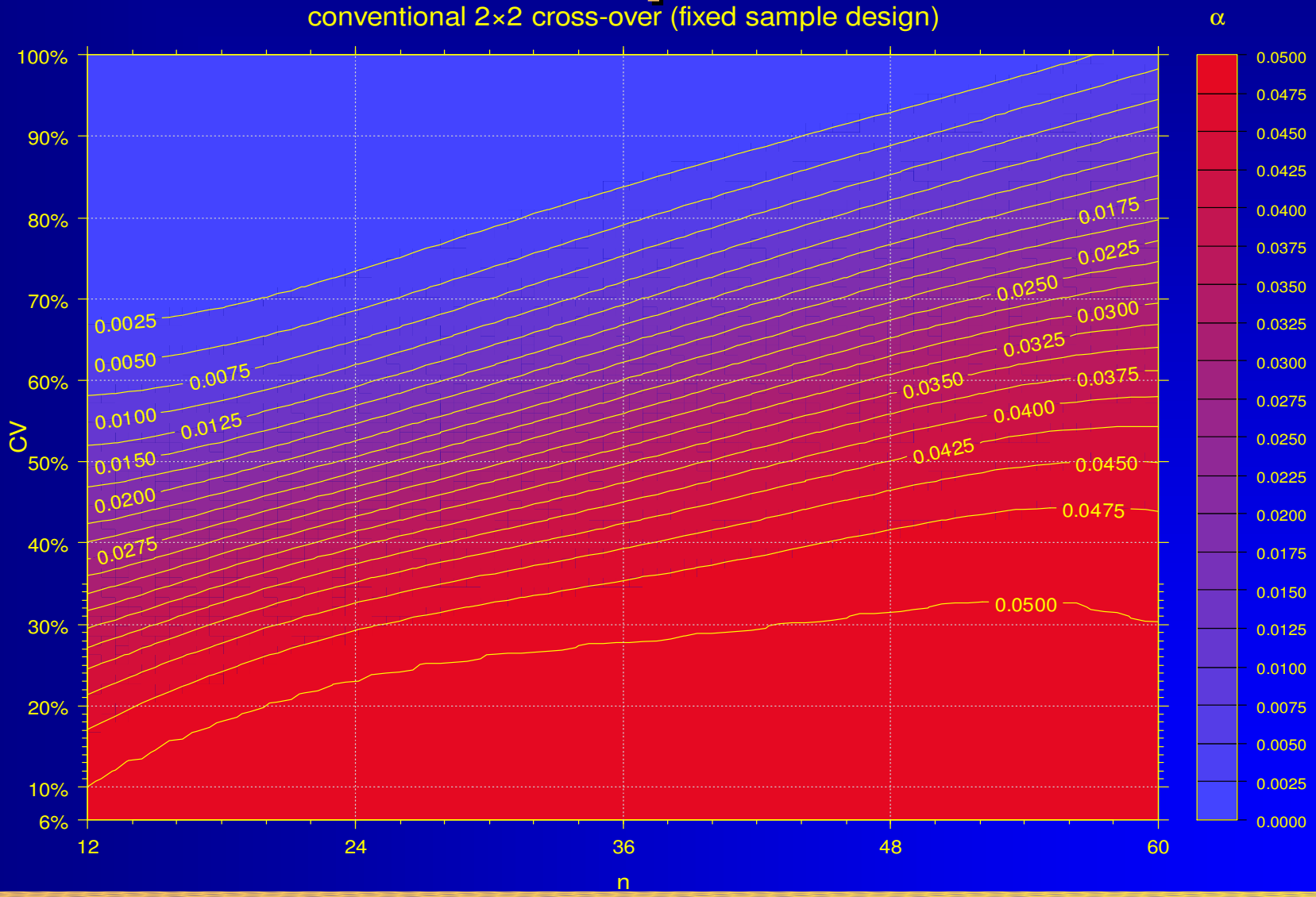
Conclusions

- Do not blindly follow guidelines. Some curent recom-mendations may lead to inflation of the patient's risk and/or deteriorate power.
- Validated frameworks can be applied without requir-ing the sponsor to perform own simulations – though they could further improve power based on additio-nal assumptions.
- Two-stage designs are both ethical and economical alternatives to fixed-sample designs.

Outlook

- Feasibility / futility rules.
- Arbitrary expected T/R and/or power.
- Methods without interim power.
- Dropping a candidate formulation from a higher-order cross-over; continue with 2×2.
- Continue a 2×2 in replicate design for scaling.
- Fully adaptive methods.
- Exact method (not depending on simulations).
- Application to replicate designs / scaling.

Don’t panic!


conventional 2×2 cross-over (fixed sample design)
α
CV
n
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
6%
12
24
36
48
60
0.0025
0.0050
0.0075
0.0100
0.0125
0.0150
0.0175
0.0200
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¡Gracias!

Two-Stage Sequential Designs in Bioequivalence

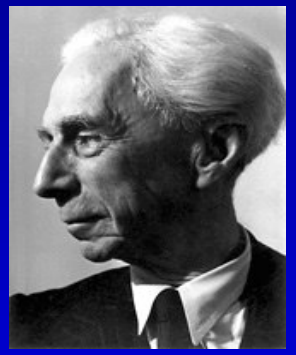
Open Questions?

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

To bear in Remembrance...

The fundamental cause of trouble in the world today is that the stupid are cocksure while
the intelligent are full of doubt.

Bertrand Russell

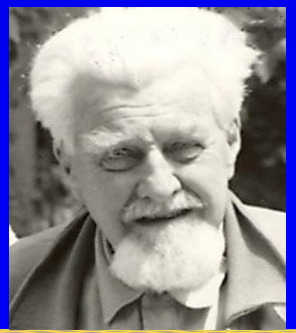


In bioequivalence we must not forget the only important – *the patient*! He/she is living person, not just α 0.05.

Dirk Marteen Barends

It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast.
It keeps him young.

Konrad Lorenz



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