Biostatistics

Sequential Designs for BE Studies

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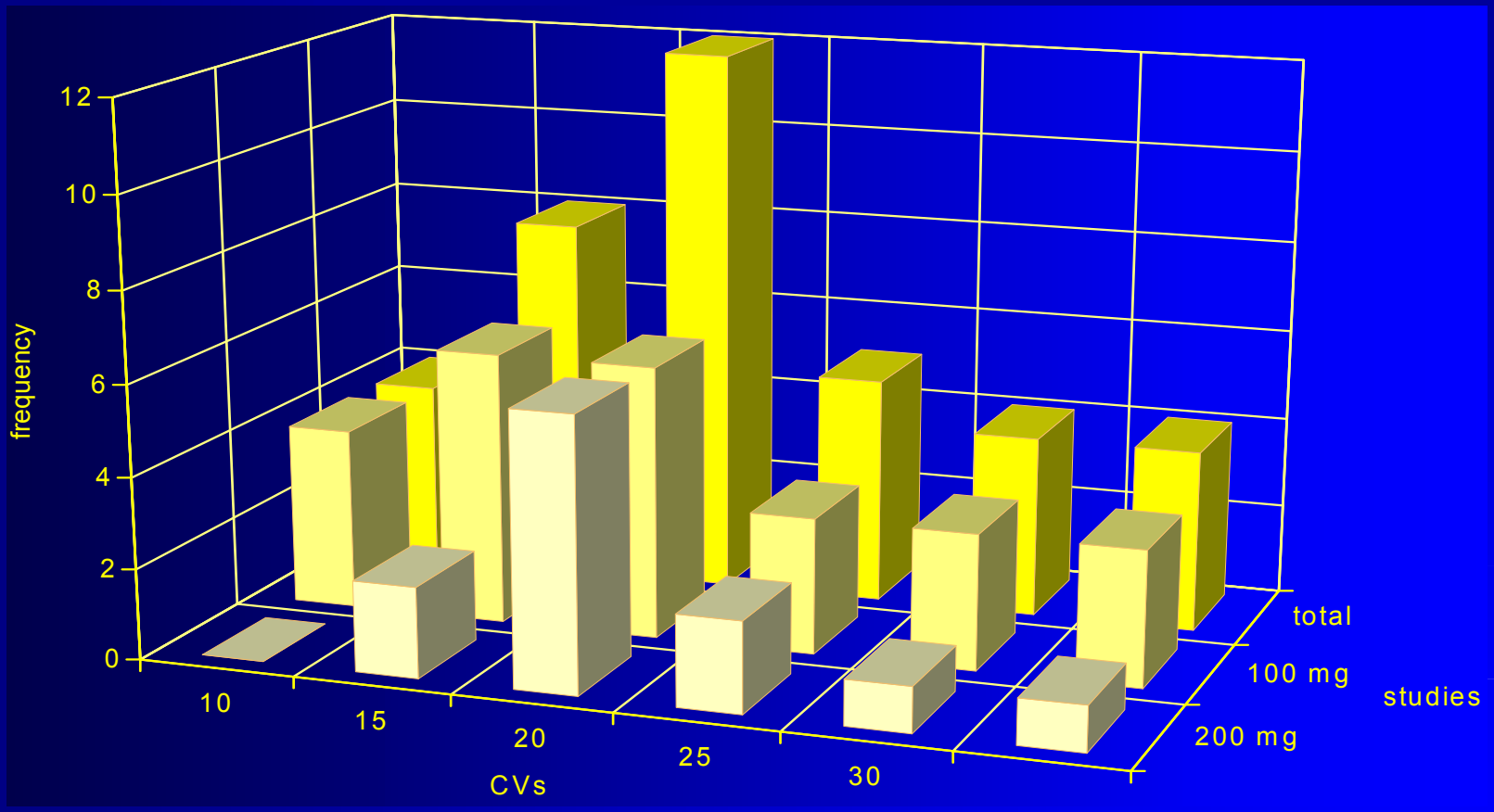
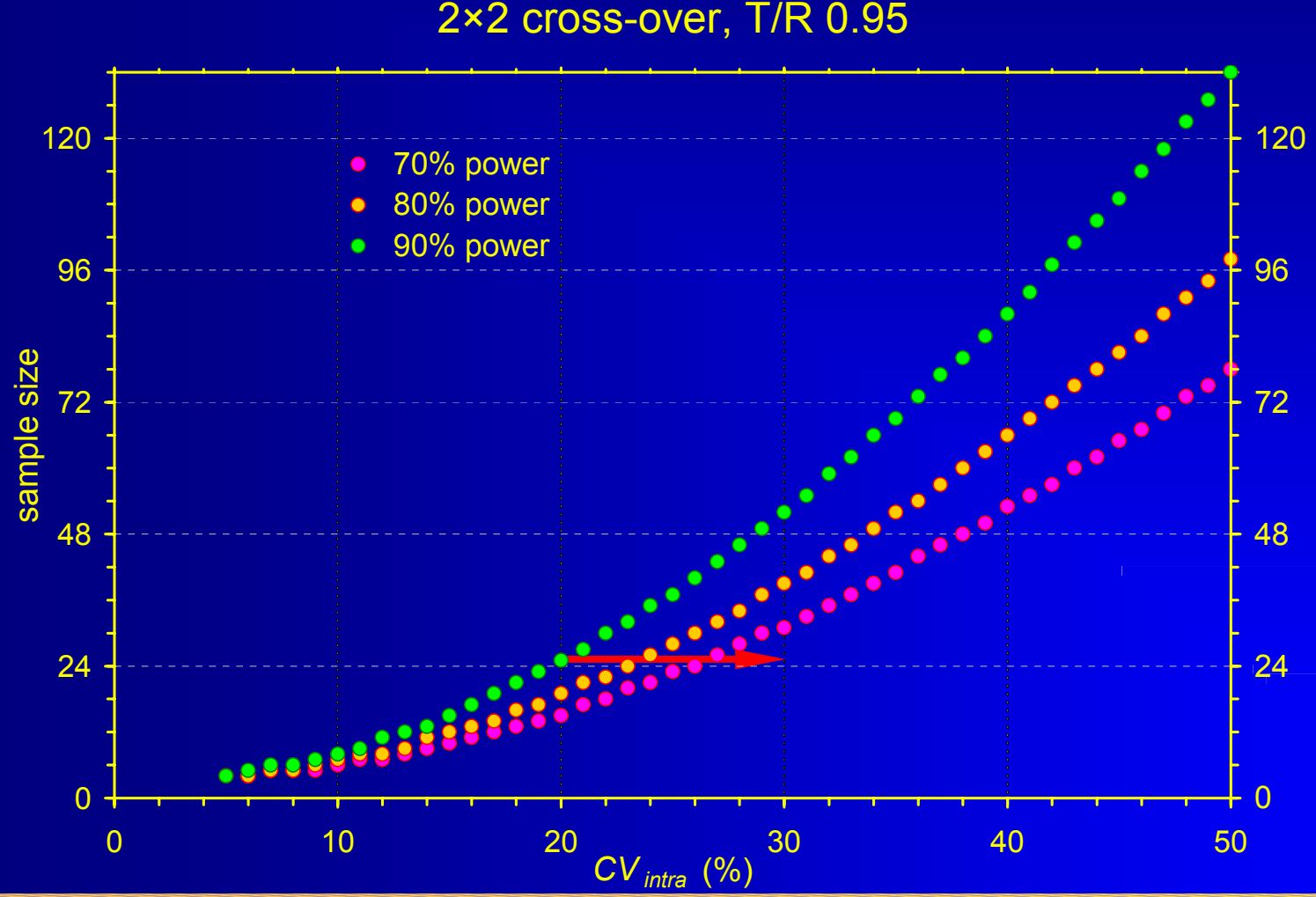
BEBAC

Published data



Doxicycline (37 studies from **Blume/Mutschler**, *Bioäquivalenz: Qualitätsbewertung wirkstoffgleicher Fertigarzneimittel*, GOVI-Verlag, Frankfurt am Main/Eschborn, 1989-1996)

CV based on assumptions!



Example: Study planned on expected 20% CV with 90% power.

If CV is 30%, power drops to only 58%…

Add-on / Two-Stage Designs

- Sometimes properly designed and executed studies fail due to
  - 'true' bioinequivalence,
  - poor study conduct (increasing variability),
  - pure chance (producer's risk hit),
  - false (over-optimistic) assumptions about variability and/or T/R-ratio.
- The patient's risk must be preserved
  - Already noticed at Bio-International Conferences (1989, 1992) and guidelines from the 1990s.

Sequential Designs

- Have a 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 & DeMets (1983), …
    - First proposal by Gould (1995) in the area of BE did not get regulatory acceptance in Europe, but
    - new methods stated in recent guidelines.

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

Sequential Designs

- Methods by Potvin *et al.* (2008) promising
  - Supported by the 'Product Quality Research Institute' (members: FDA/CDER, Health Canada, USP, AAPS, PhRMA…)
    - Three of BEBAC's protocols accepted by German BfArM, one product approved in 06/2011.

Potvin D, Diliberti CE, Hauck WW, Parr AF, Schuirmann DJ, and RA Smith
Sequential design approaches for bioequivalence studies with crossover designs
Pharmaceut Statist 7/4, 245–62 (2008), DOI: 10.1002/pst.294
http://www3.interscience.wiley.com/cgi-bin/abstract/115805765/ABSTRACT

Review of Guidelines

- Canada (May 2012)

  Potvin *et al.* Method C recommended.

- FDA (Jun 2012)

  Potvin *et al.* Method C recommended.
  API specific guidances: Loteprednol, Dexamethasone / Tobramycin.

- EMA (Jan 2010)

  Acceptable; Potvin *et al.* Method B preferred.

- Russia (Draft 2011)

  Acceptable (Methods B and C).

Two-Stage Design

- EMA GL on BE (2010)
  - Section 4.1.8
    - Initial group of subjects treated and data analysed.
    - If BE not been demonstrated an additional group can be recruited and the results from both groups combined in a final analysis.
    - Appropriate steps to preserve the overall type I error (patient's risk).
    - Stopping criteria should be defined *a priori*.
    - First stage data should be treated as an interim analysis.

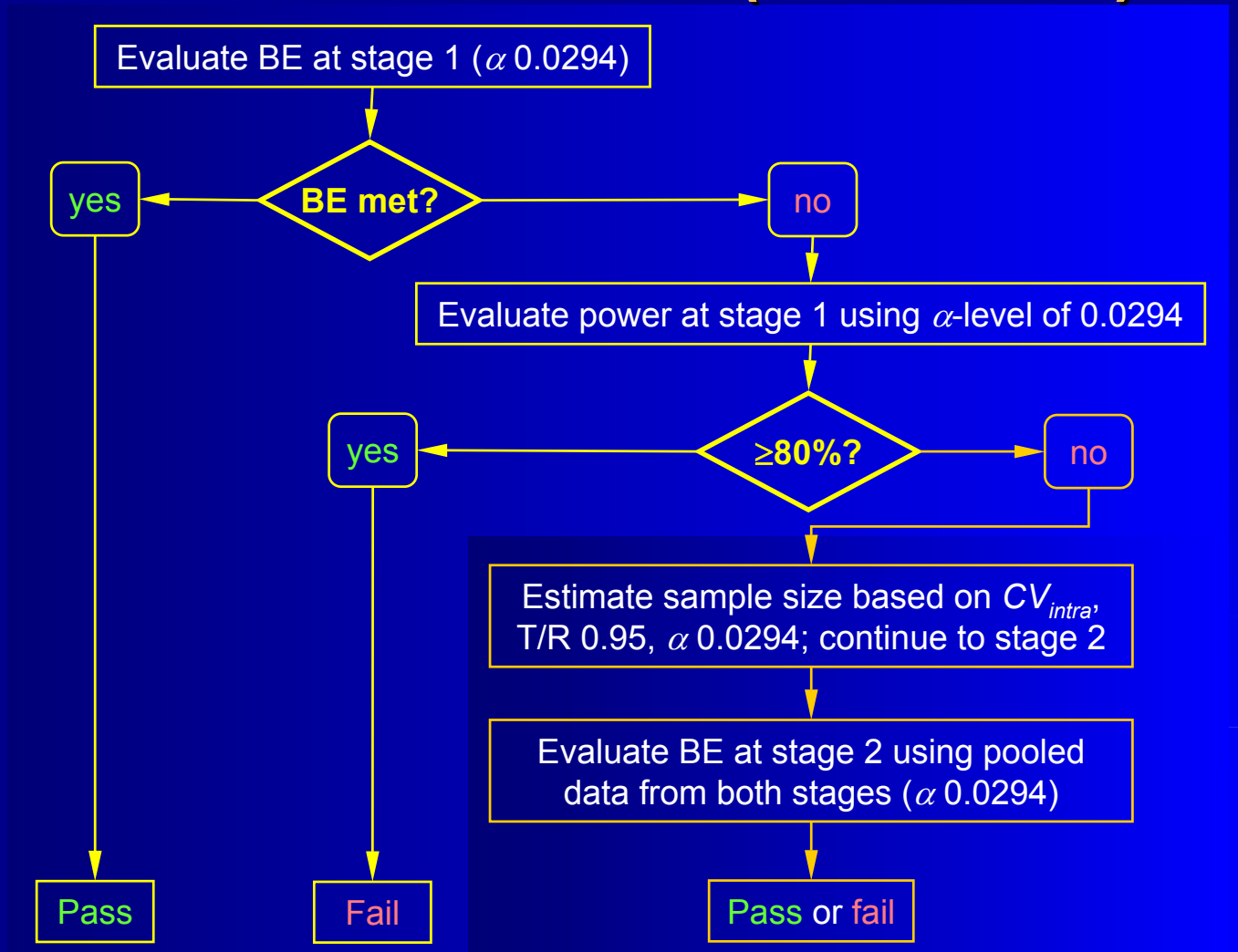
Two-Stage Design

- EMA GL on BE (2010)
  - Section 4.1.8 (cont'd)
    - Both analyses conducted at adjusted significance levels (with the confidence intervals accordingly using an adjusted coverage probability which will be higher than 90%). […] 94.12% confidence intervals for both the analysis of stage 1 and the combined data from stage 1 and stage 2 would be acceptable, but there are many acceptable alter-natives and the choice of how much alpha to spend at the interim analysis is at the company's discretion.

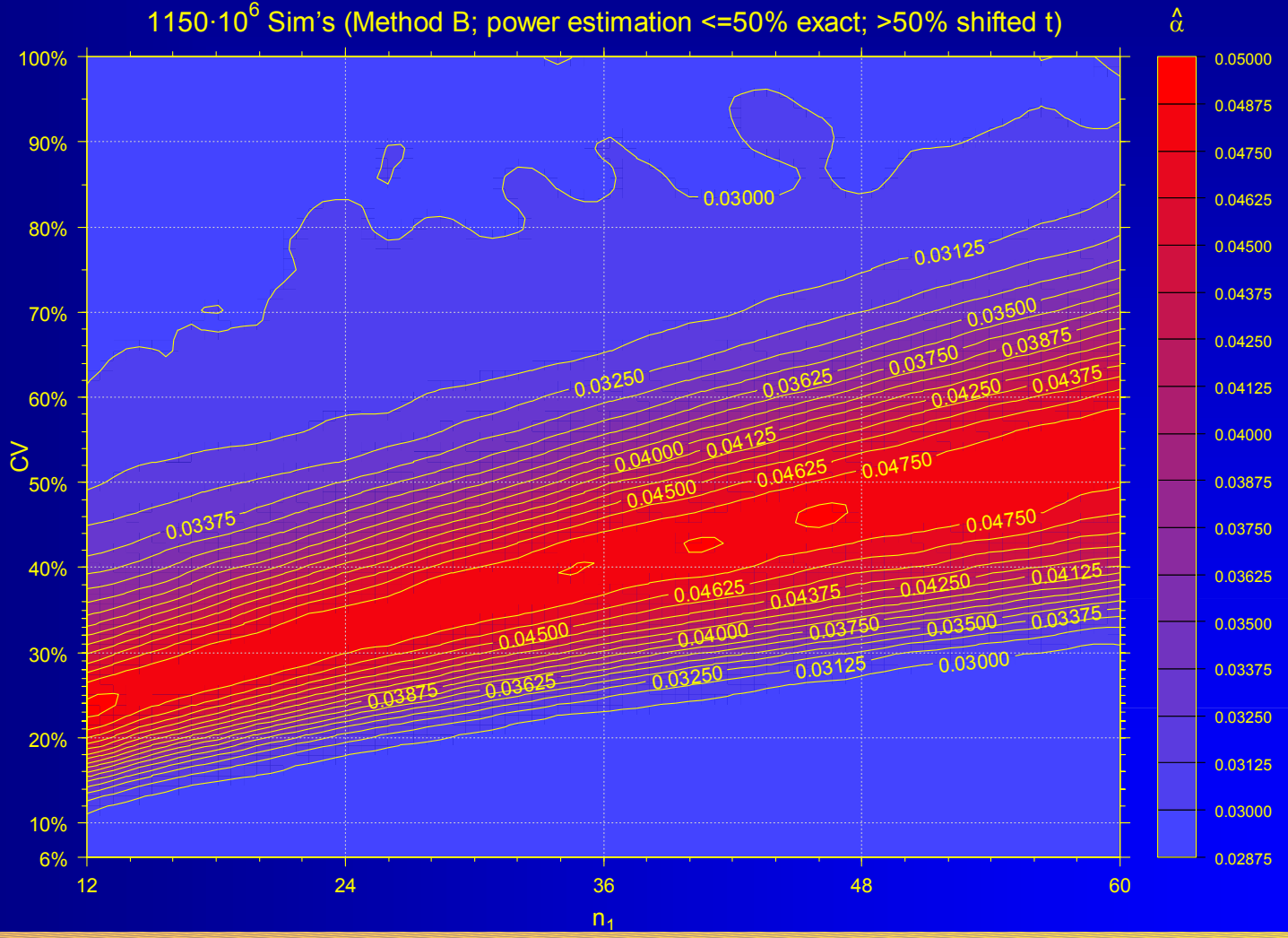
Two-Stage Design

- EMA GL on BE (2010)
  - Section 4.1.8 (cont'd)
    - Plan to use a two-stage approach must be pre-specified in the protocol along with the adjusted significance levels to be used for each of the analyses.
    - When analysing the combined data from the two stages, a term for stage should be included in the ANOVA model.

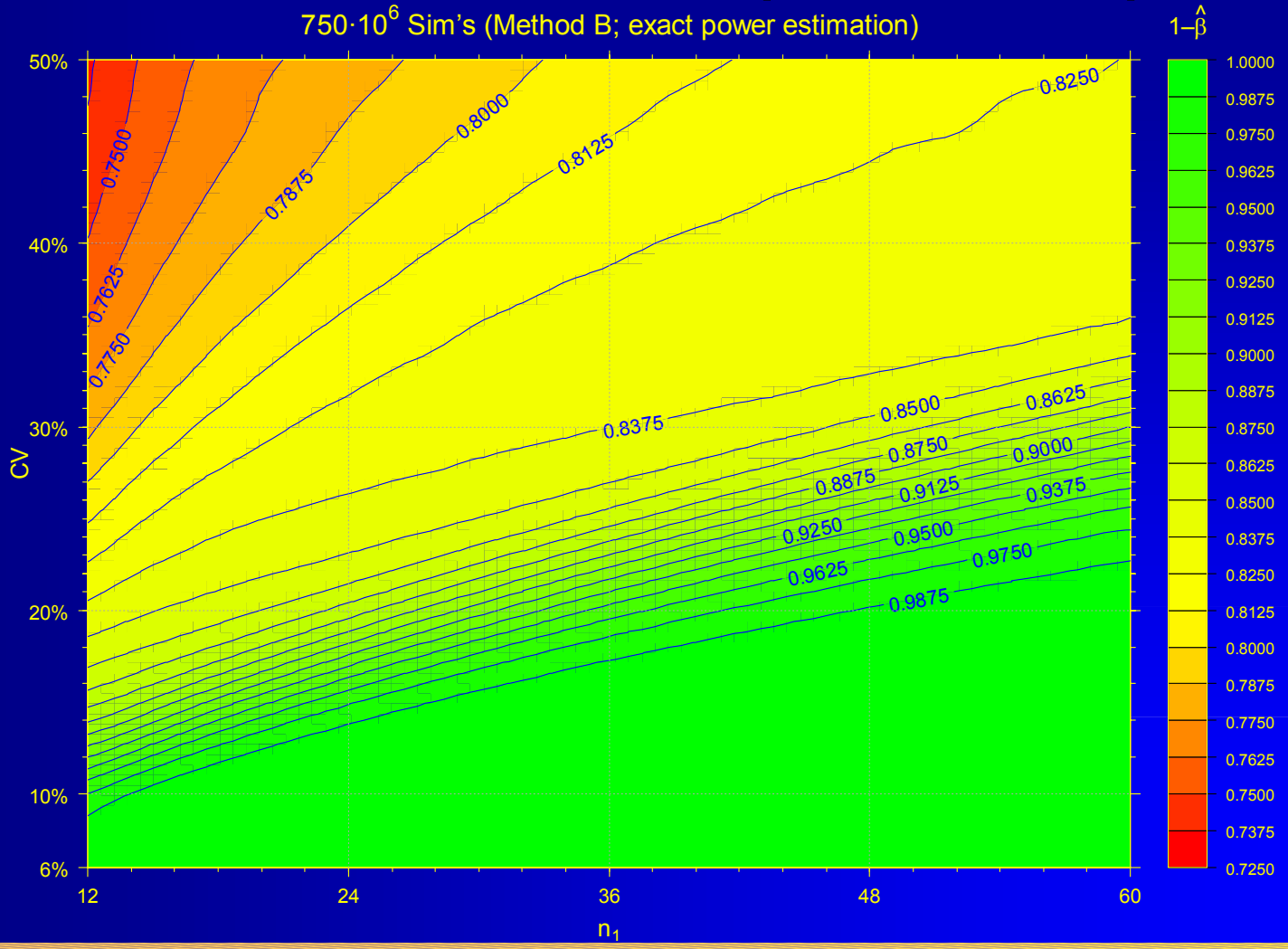
Potvin *et al.* (Method B)



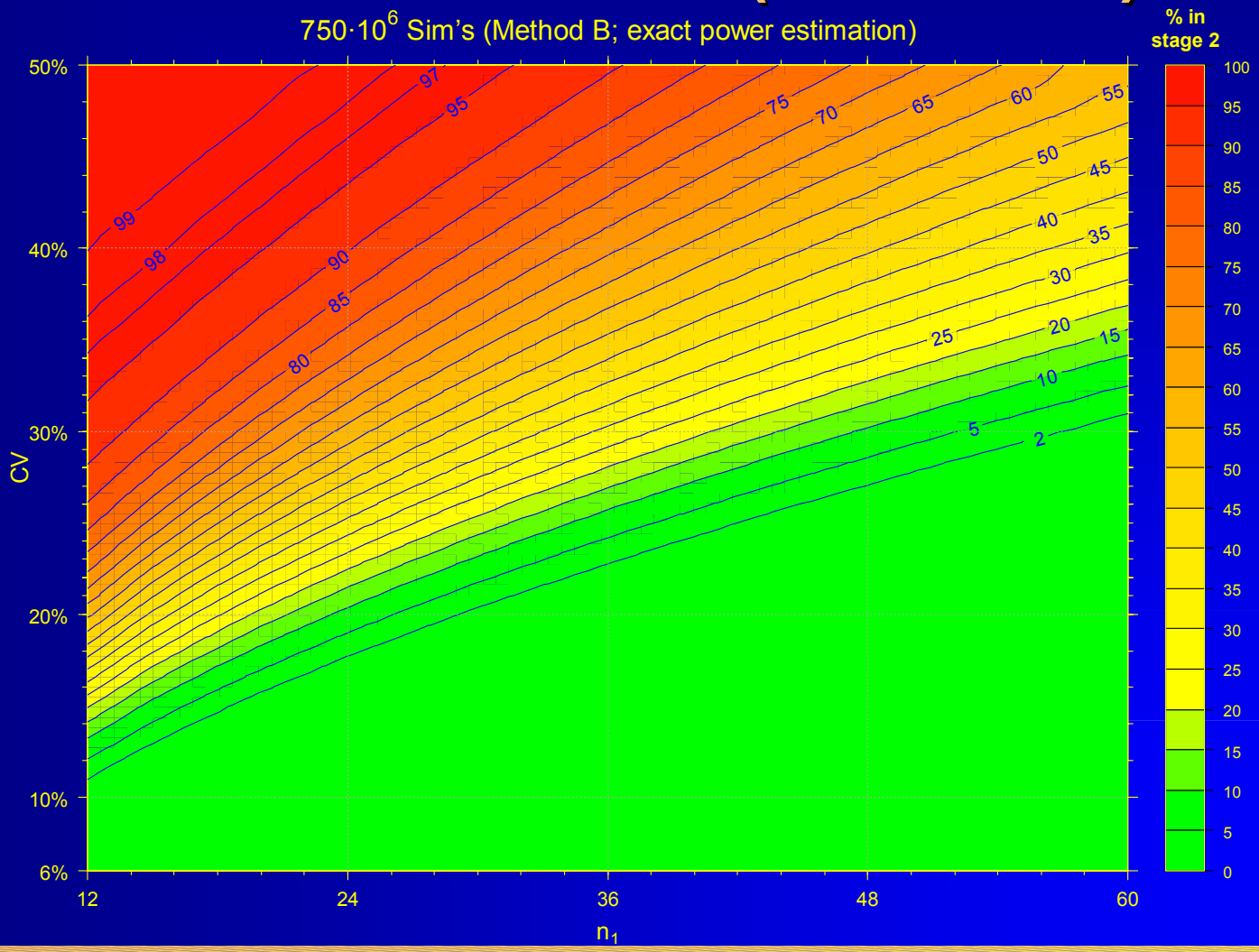
Potvin *et al.* (Method B)



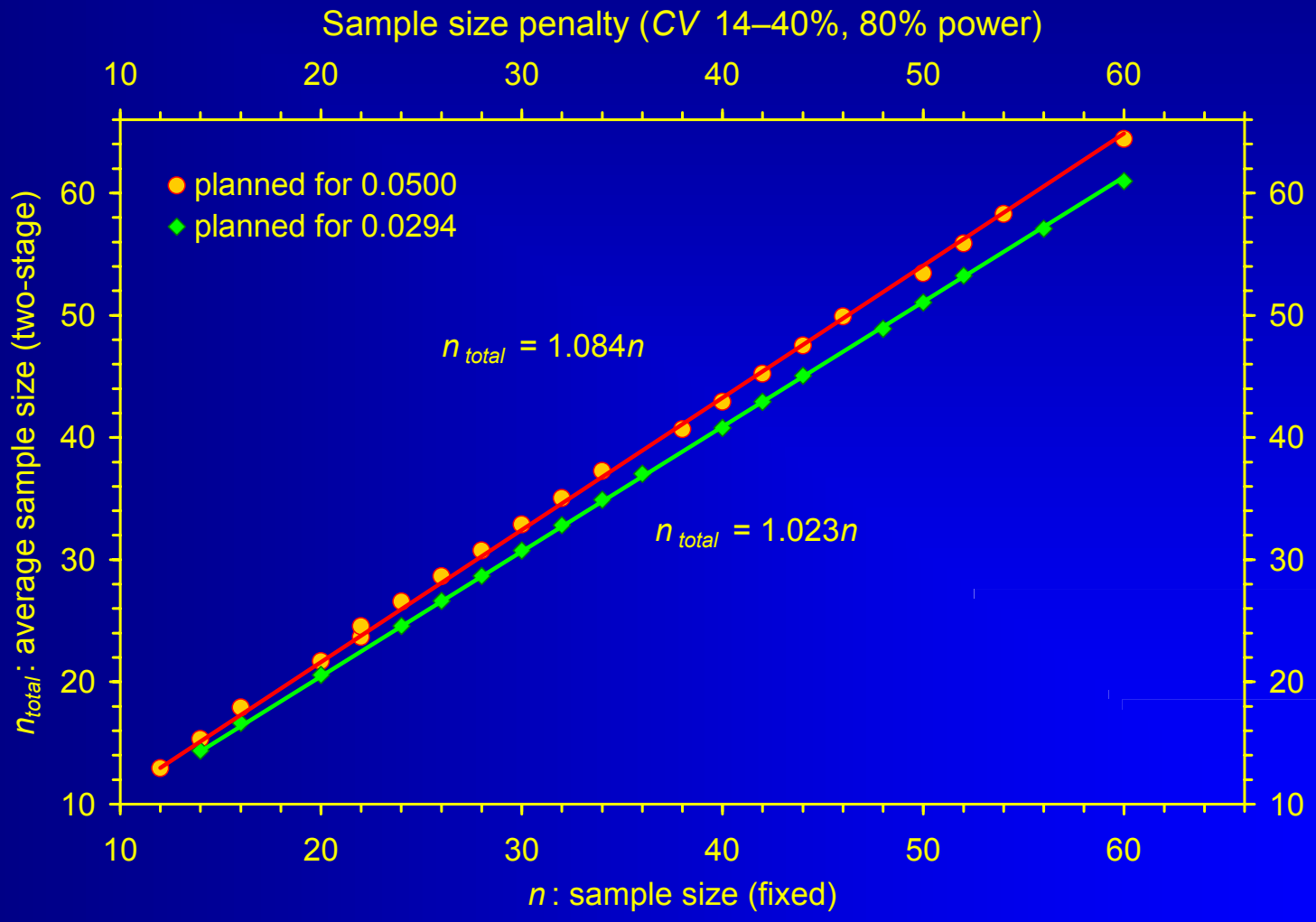
Potvin *et al.* (Method B)



Potvin *et al.* (Method B)



Potvin *et al.* (Method B)



Potvin *et al.* (Method B)

- Technical Aspects
  - Only *one* Interim Analysis (after stage 1).
  - Use software (wide step sizes in Diletti's tables); preferrable the exact method (avoid approxi-mations).
  - Should be termed 'Interim Power Analysis' *not* 'Bioequivalence Assessment' in the protocol.
  - No *a posteriori* Power – only a validated method in the decision tree.
  - No adjustment for T/R observed in stage 1 (not fully adaptive).

Potvin *et al.* (Method B)

- Technical Aspects (cont'd)
  - No futility rule preventing to go into stage 2 with a very high sample size! Must be clearly stated in the protocol (unfamiliar to the IEC because common in Phase III).
  - Pocock's α 0.0294 is used in stage 1 and in the pooled analysis (data from stages 1 + 2), *i.e.*, the 1 – 2×α = 94.12% CI is calculated.
  - Overall patient's risk preserved at ≤0.05.

Potvin *et al.* (Method B)

- 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)

- Technical Aspects (cont'd)
  - Potvin *et al.* used a simple approximative power estimation based on the shifted t-distribution.
  - If possible use the exact method (Owen; *R* package *PowerTOST* `method = 'exact'`) or at least one based on the noncentral t-distribution (*PowerTOST* `method = 'noncentral'`).
  - Power obtained in stage 1 (example 2 from Potvin):

method	power
approx. (shifted t)	50.49%
approx. (noncentral t)	52.16%
exact	52.51%

Potvin *et al.* (Method B)

```
Model Specification and User Settings
       Dependent variable : Response
                Transform : LN
            Fixed terms : int+Sequence+Period+Treatment
    Random/repeated terms : Sequence*Subject

Final variance parameter estimates:
    Var(Sequence*Subject)     0.408682
          Var(Residual)     0.0326336
        Intrasubject CV     0.182132

Bioequivalence Statistics
User-Specified Confidence Level for CI's = 94.1200
Percent of Reference to Detect for 2-1 Tests = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250
Reference: Reference   LSMean = 0.954668  SE = 0.191772  GeoLSM = 2.597808
----------------------------------------------------------------------
Test:      Test        LSMean = 1.038626  SE = 0.191772  GeoLSM = 2.825331

    Difference  =   0.0840,  Diff_SE = 0.0737,  df = 10.0
    Ratio(%Ref) = 108.7583

                      Classical
CI User = (   92.9330,  127.2838)
Failed to show average bioequivalence for confidence=94.12 and percent=20.0.
```

12 subjects in stage 1, conventional BE model

CV_{intra} 18.2%

α 0.0294

Failed with 94.12% Confidence Interval

Potvin *et al.* (Method B)

```
require(PowerTOST)
power.TOST(alpha=0.0294, theta0=0.95,
           CV=0.182132, n=12, design='2x2',
           method='exact')

[1] 0.5251476
```

α 0.0294, T/R 95% – *not* 108.76% observed in stage 1!
CV_{intra} 18.2%, 12 subjects in stage 1

Power 52.5% – initiate stage 2

```
sampleN.TOST(alpha=0.0294, targetpower=0.80, logscale=TRUE,
             theta1=0.8, theta2=1.25, theta0=0.95,
             CV=0.182132, design='2x2', method='exact',
             print=TRUE)

++++++++++++ Equivalence test - TOST ++++++++++++
             Sample size estimation
-----------------------------------------------
Study design:  2x2 crossover
log-transformed data (multiplicative model)

alpha = 0.0294, target power = 0.8
BE margins        = 0.8 ... 1.25
Null (true) ratio = 0.95,  CV = 0.182132

Sample size
 n     power
20   0.829160
```

Estimate total sample size:
α 0.0294, T/R 95%, CV_{intra} 18.2%, 80% power

Total sample size 20: include another 8 in stage 2

Potvin *et al.* (Method B)

```
Model Specification and User Settings
      Dependent variable : Cmax (ng/mL)
               Transform : LN
           Fixed terms : int+Stage+Sequence+Period(Stage)+Treatment
   Random/repeated terms : Sequence*Stage*Subject

Final variance parameter estimates:
Var(Sequence*Stage*Subject)    0.518978
          Var(Residual)        0.0458956
        Intrasubject CV        0.216714

Bioequivalence Statistics
User-Specified Confidence Level for CI's = 94.1200
Percent of Reference to Detect for 2-1 Tests = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250
Formulation variable: Treatment
Reference: Reference   LSMean = 1.133431  SE = 0.171385  GeoLSM = 3.106297
-------------------------------------------------------------------------
Test:      Test        LSMean = 1.147870  SE = 0.171385  GeoLSM = 3.151473

    Difference  =   0.0144,  Diff_SE = 0.0677,  df = 17.0
    Ratio(%Ref) = 101.4544

                      Classical
    CI  90% = (   90.1729,  114.1472)
    CI User = (   88.4422,  116.3810)
    Average bioequivalence shown for confidence=94.12 and percent=20.0.
```

8 subjects in stage 2 (20 total), modified model in pooled analysis

α 0.0294 in pooled analysis

BE shown with 94.12% CI; overall $\alpha \leq 0.05$!

Potvin *et al.* (Method B – EMA)

```
Model Specification and User Settings
      Dependent variable : Cmax (ng/mL)
               Transform : LN
           Fixed terms : int+Stage+Sequence+Sequence*Stage
                         +Sequence*Stage*Subject+Period(Stage)+Treatment

Final variance parameter estimates:
Var(Sequence*Stage*Subject)   0.549653
          Var(Residual)       0.0458956
        Intrasubject CV       0.216714

Bioequivalence Statistics
User-Specified Confidence Level for CI's = 94.1200
Percent of Reference to Detect for 2-1 Tests = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250
Formulation variable: Treatment
Reference: Reference   LSMean = 1.133431  SE = 0.171385  GeoLSM = 3.106297
-------------------------------------------------------------------------
Test:      Test        LSMean = 1.147870  SE = 0.171385  GeoLSM = 3.151473

    Difference  =   0.0144,  Diff_SE = 0.0677,  df = 17.0
    Ratio(%Ref) = 101.4544

                      Classical
    CI  90% = (   90.1729,  114.1472)
    CI User = (   88.4422,  116.3810)
    Average bioequivalence shown for confidence=94.12 and percent=20.0.
```

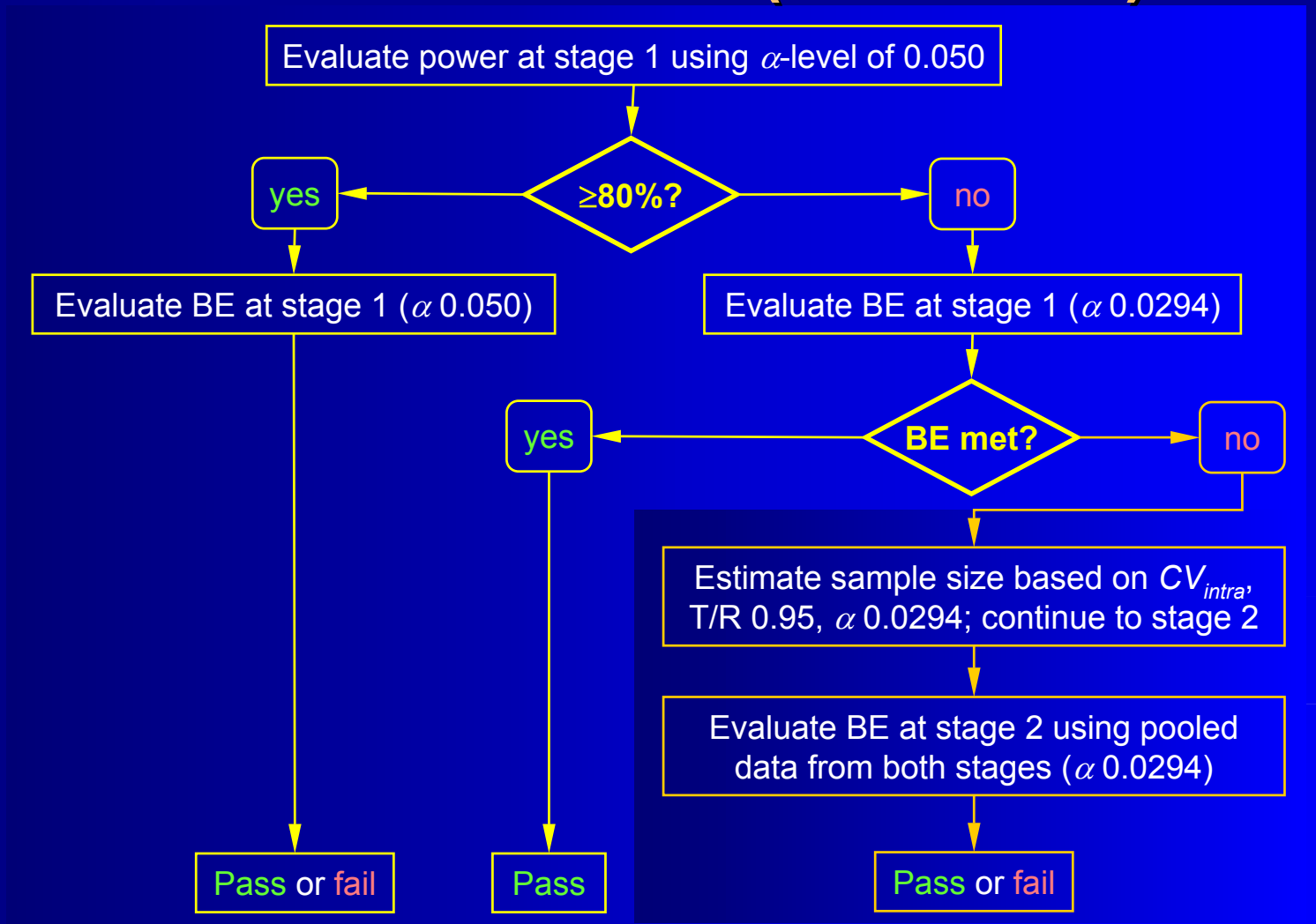
8 subjects in stage 2 (20 total), modified model in pooled analysis

Q&A March 2013

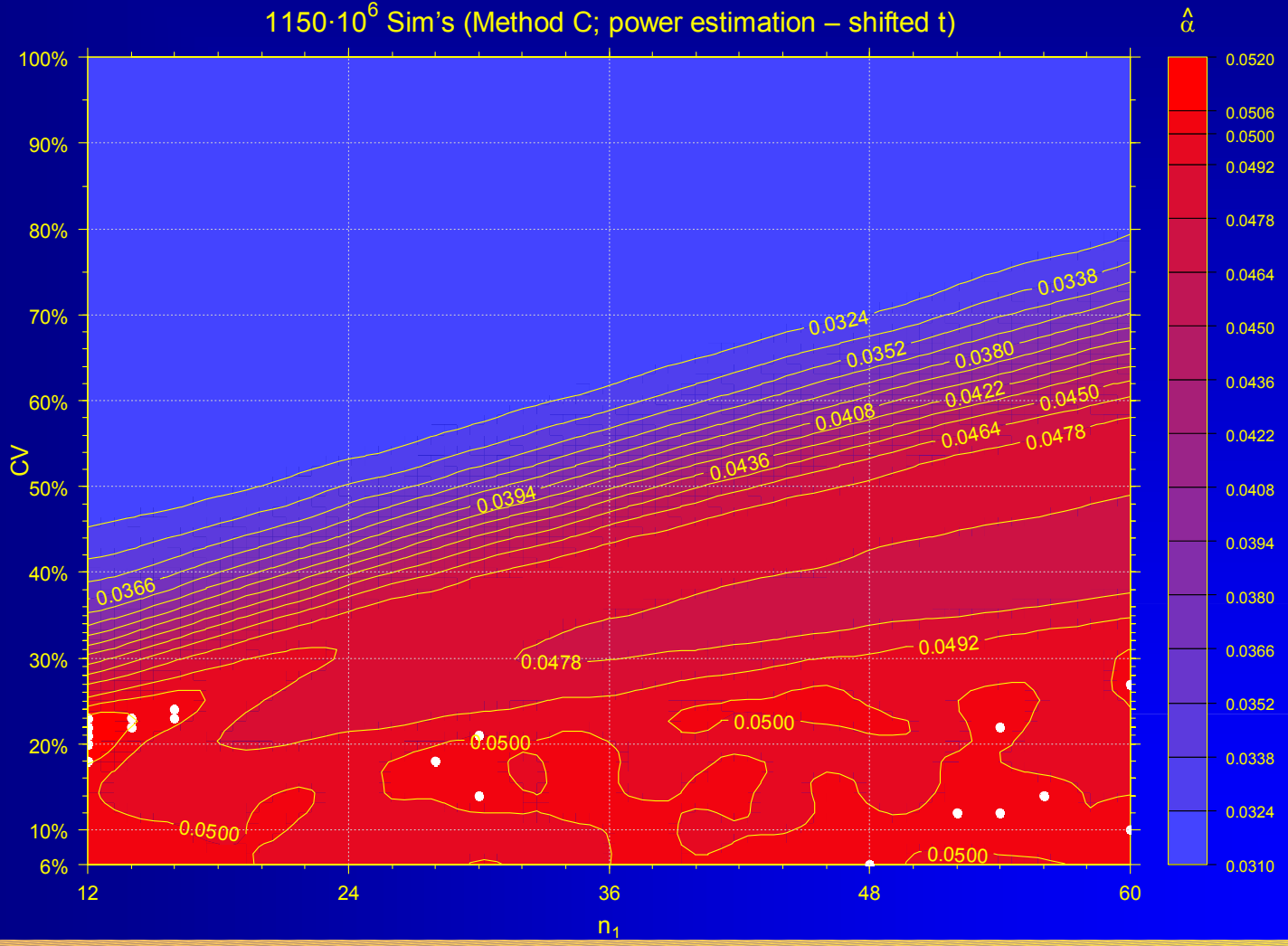
α 0.0294 in pooled analysis

BE shown with 94.12% CI; overall $\alpha \leq 0.05$!

Potvin *et al.* (Method C)



Potvin *et al.* (Method C)



Potvin *et al.* (Method B *vs.* C)

- Pros & cons
  - Method C (*if power ≥80%!*) is a conventional BE study; no penality 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 go to stage 2 almost all the time; total sizes are similar.
  - Method B slightly more conservative than C.

Potvin *et al.* (Method B *vs.* C)

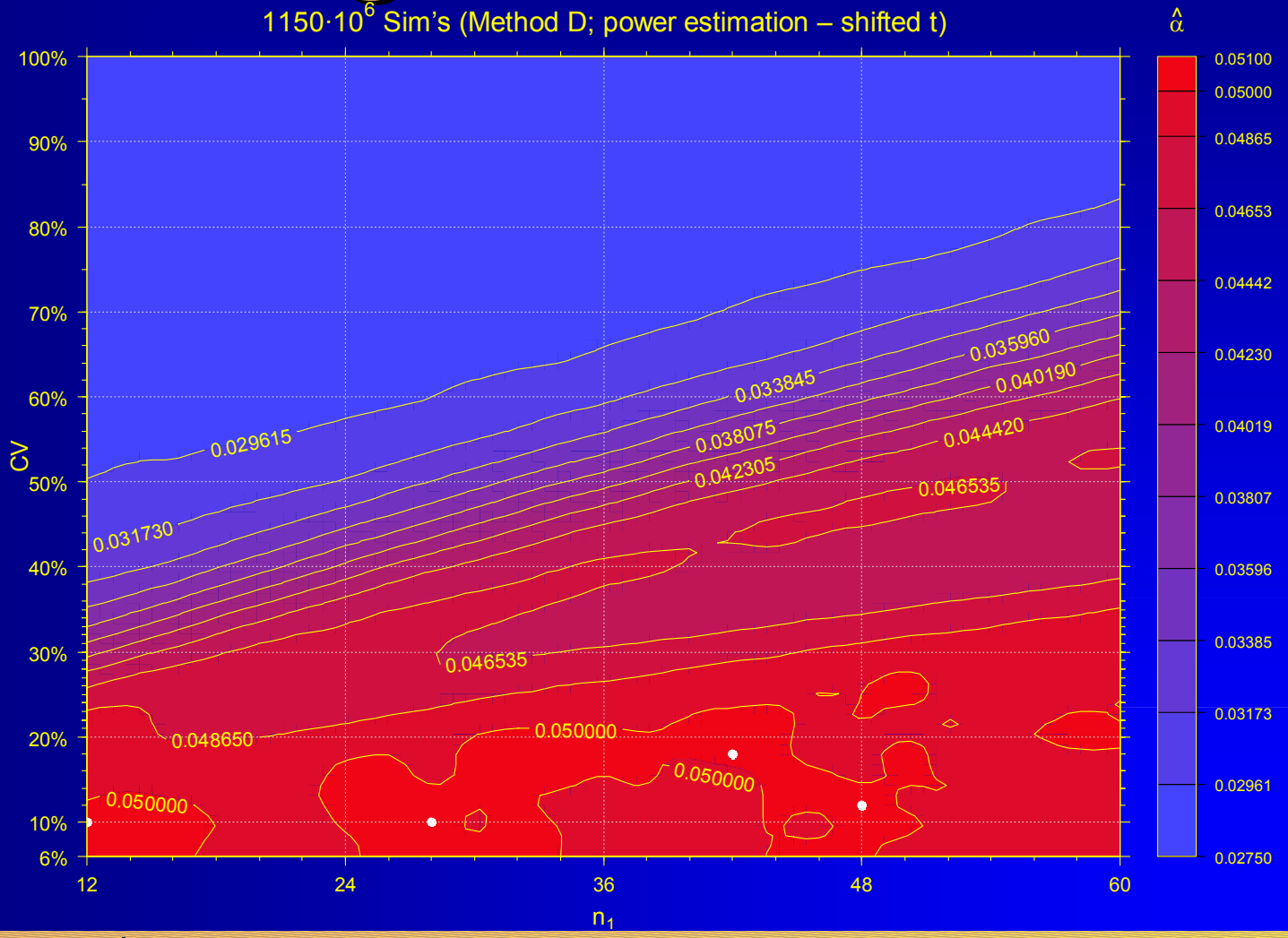
- Recommendations
  - Method C preferred due to slightly higher power than method B (FDA, HPB). Method B for EMA.
  - Plan the study *as if* the CV is known
    - If assumptions turn out to be true = no penalty
    - If lower power (CV_{intra} higher than expected), BE still possible in first stage (penalty; 94.12% CI) or continue to stage 2 as a 'safety net'.
  - Don't jeopardize! Smaller sample sizes in the first stage than in a fixed design don't pay off. Total sample sizes are ~10–20% higher.

Sequential Designs

- Methods by Potvin *et al.* (2008) limited to T/R of 0.95 and 80% power
  - Follow-up paper 2011
    - T/R 0.90 instead of 0.95.
    - Method D (like C, but α 0.0280 instead of α 0.0294).
    - Might be useful if T/R 0.95 and power 90% as well; *not validated yet!* Simulations required.

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'
Pharmaceut Statist 11/1, 8–13 (2011), DOI: 10.1002/pst.483

Montague *et al.* (Method D)



Case Studies (EMA)

- Method C: Study passed in first stage (49 subjects, CV 30.65%, 90% CI)
  - Deficiency 1: Unadjusted α in stage 1 not acceptable
    - Response 1: Study passed with 94.12% CI (*post hoc* switch to Method B).
  - Deficiency 2: 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.
    - Response 2: One million simulations based on study's sample size and CV.
      α_{emp} 0.0494 (95% CI: 0.0490 – 0.0498)

Case Studies (EMA)

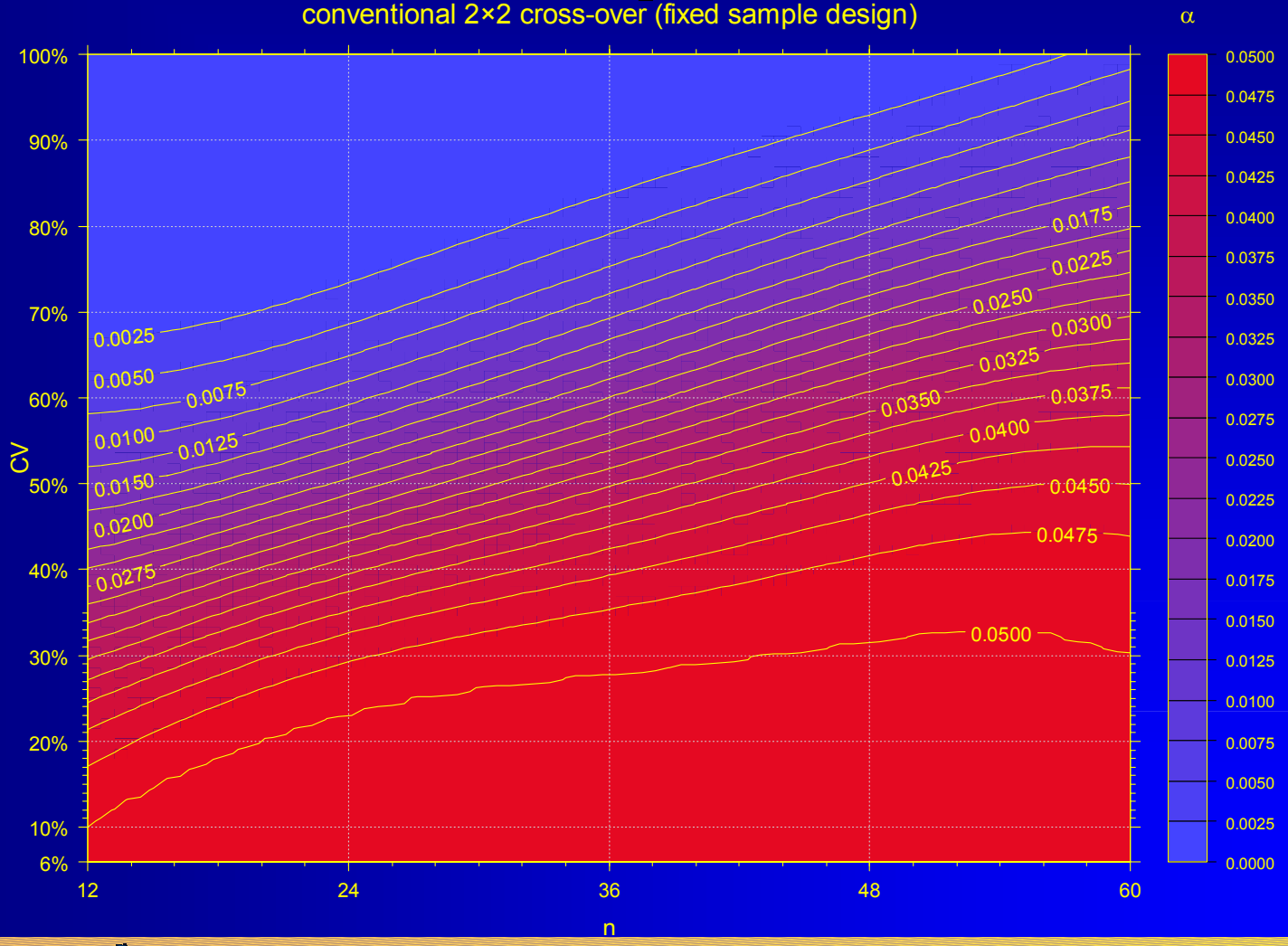
- Method C: Study stopped in first stage
  AUC power >80%, passed with 90% CI
  C_{max} power <80%, passed with 94.12% CI
  - Deficiency: Adapting the confidence intervals based upon power is not acceptable and also not in accordance with the EMA guideline. Confidence intervals should be selected *a priori*, without evaluation of the power. Therefore, the applicant should submit the 94.12% confidence intervals for AUC.
    - Pending: AUC fails with 94.12% CI…

Outlook

- Feasibility / futility rules.
- Arbitrary expected T/R and/or power.
- Methods without interim power.
- Application to parallel designs.
- Dropping a candidate formulation from a higher-order cross-over; continue with 2×2.
- Exact method (not requiring simulations).
- Adaption for T/R observed in stage 1 (full adaptive design).

Don’t panic!

conventional 2×2 cross-over (fixed sample design)



Thank You!

Sequential Designs for BE Studies

Open Questions?

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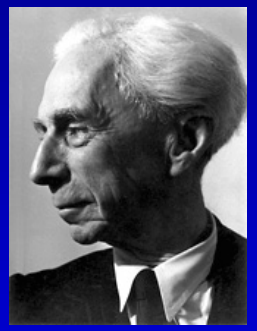
Dedicated to the memory of Dirk Maarten Barends (1945 – 2012).

To bear in Remembrance...

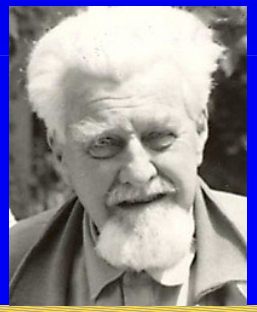
The fundamental cause of trouble in the world today is that the stupid are cocksure
while the intelligent are full of doubt. *Bertrand Russell*



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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