BE
BAC

Biostatistics
Two-Stage Designs

Helmut Schütz
BEBAC

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α **and** β

● All formal decisions are subjected to two types of error:

   ■ α Probability of Error Type I (aka Risk Type I)
   ■ β Probability of Error Type II (aka Risk Type II)
     Example from the justice system:

Verdict	Defendant innocent	Defendant guilty
Presumption of innocence not accepted (guilty)	Error type I	Correct
Presumption of innocence accepted (not guilty)	Correct	Error type II

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α and β

- Or in more statistical terms:

Decision	Null hypothesis true	Null hypothesis false
Null hypothesis rejected	**Error type I**	**Correct (H_a)**
Failed to reject null hypothesis	**Correct (H_0)**	**Error type II**

- In BE-testing the null hypothesis is bio<u>in</u>equivalence ($\mu_1 \neq \mu_2$)!

Decision	Null hypothesis true	Null hypothesis false
Null hypothesis rejected	**Patients' risk**	**Correct (BE)**
Failed to reject null hypothesis	**Correct (not BE)**	**Producer's risk**

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α ...

- ●**Patient's Risk** to be treated with an inequivalent formulation $(H_0$ falsely rejected)
  - ■BA of the test compared to reference in a *particular* patient is risky *either* below 80% *or* above 125%.
  - ■If we keep the risk of particular patients at α 0.05 (5%), the risk of the entire population of patients $(<80\%$ *and* $>125\%)$ is 2×α (10%) – expressed as: 90% CI = 1 – 2×α = 0.90

95% one-sided CI	**95% one-sided CI**	**90% two-sided CI = two 95% one-sided**
0.6 0.8 1 1.25 1.67	0.6 0.8 1 1.25 1.67	0.6 0.8 1 1.25 1.67
particular patient	particular patient	population of patients

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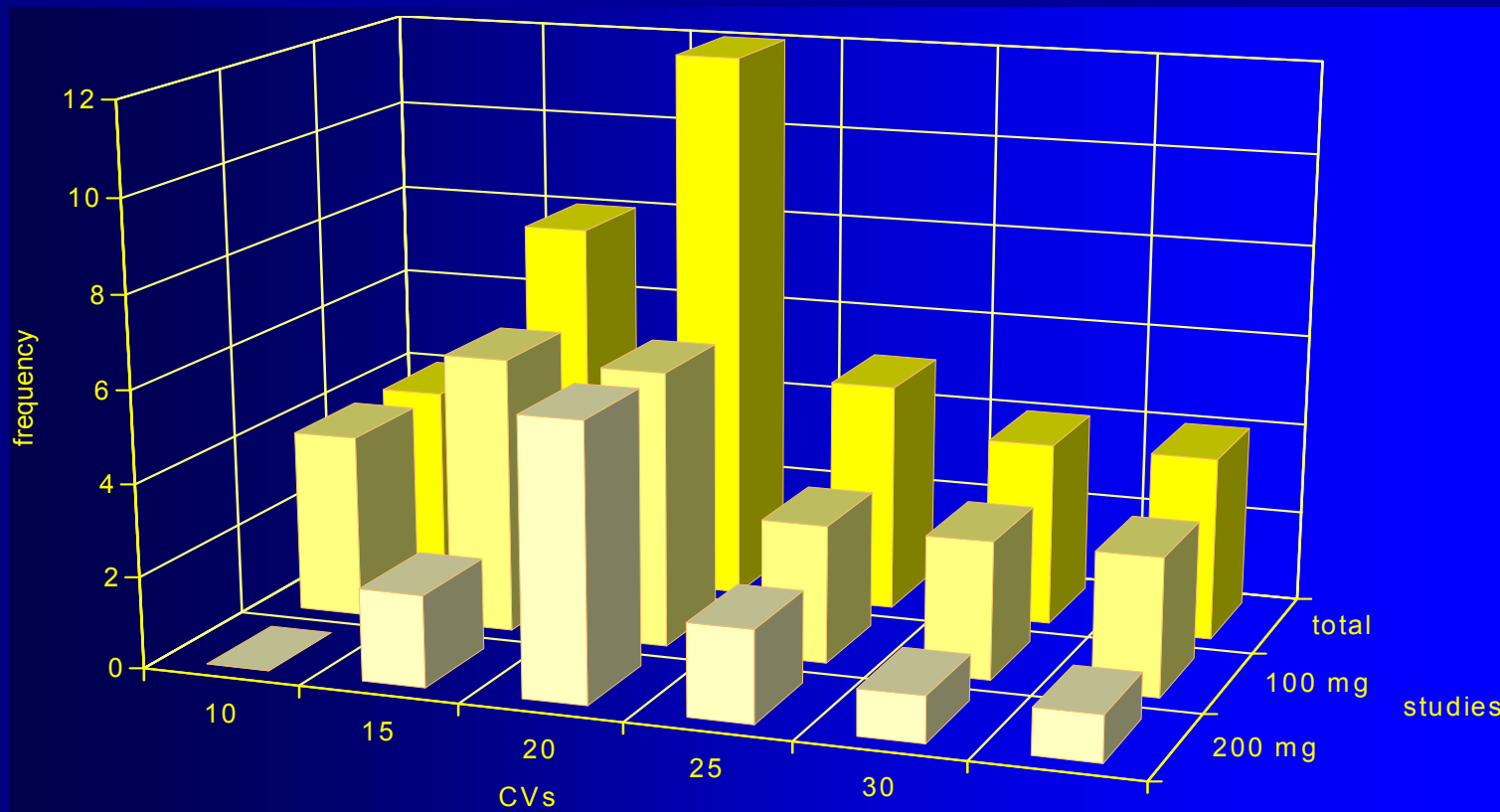
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… and β
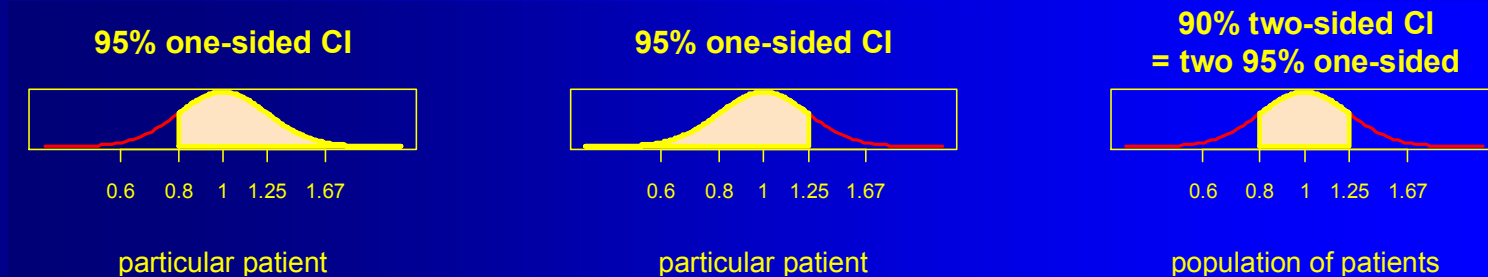
● Producer's Risk to get no approval for a equivalent formulation (H_0 falsely not rejected)

  ■ *Set* in study planning to ≤0.2 (20%), where power = 1 – β = ≥80%

  ■ If power is set to 80 %,
       one out of five studies will fail just by chance!

α 0.05	BE
not BE	β 0.20

← 0.20 = 1/5

  ■ *A posteriori* (*post hoc*) power does not make sense!
       Either a study has demonstrated BE or not.

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Published data

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

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Sample Size (Guidelines)

- Recommended minimum
  - 12 WHO, EU, CAN, NZ, AUS, AR, MZ, ASEAN States, RSA, Russia (2011 Draft)
  - 12 USA 'A pilot study that documents BE can be appropriate, provided its design and execution are suitable and a sufficient number of subjects (*e.g.*, 12) have completed the study.'
  - 18 Russia (2008)
  - 20 RSA (MR formulations)
  - 24 Saudia Arabia (12 to 24 if statistically justifiable)
  - 24 Brazil
  - 'Sufficient number' Japan

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Sample Size (Limits)

- **Maximum**
  - ■ NZ: If the calculated number of subjects appears to be higher than is ethically justifiable, it may be necessary to accept a statistical power which is less than desirable. Normally it is not practical to use more than about 40 subjects in a bioavailability study.
  - ■ All others: Not specified (judged by IEC/IRB or local Authorities).
    ICH E9, Section 3.5 applies: *"The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed."*

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EMEA

● NfG on the Investigation of BA/BE (2001)

■ The number of subjects required is determined by

- the error variance associated with the primary characteristic to be studied as estimated from
  - ➢ a pilot experiment,
  - ➢ previous studies, or
  - ➢ published data,
- the significance level desired,
- the expected deviation (Δ) from the reference product compatible with BE and,
- the required power.

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EMA

- BE Guideline (2010)
  - The number of subjects to be included in the study should be based on an *appropriate* sample size calculation.
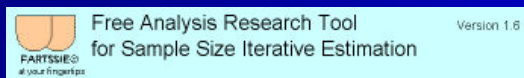
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Tools

- Sample Size Tables (Phillips, Diletti, Hauschke, Chow, Julious, …)

- Approximations (Diletti, Chow, Julious, …)

- General purpose (SAS, S+, R, StaTable, …)

- Specialized Software (nQuery Advisor, PASS, FARTSSIE, StudySize, …)

- Exact method (Owen – implemented in R-package $PowerTOST$)[*]

* Thanks to Detlew Labes!

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Approximations obsolete

- Exact sample size tables still useful in checking plausibility of software's results
- Approximations based on noncentral *t* (FARTSSIE17)

Free Analysis Research Tool
for Sample Size Iterative Estimation   Version 1.6

http://individual.utoronto.ca/ddubins/FARTSSIE17.xls
or ℝ / S+ →

- Exact method (Owen) in *R*-package *PowerTOST*

http://cran.r-project.org/web/packages/PowerTOST/
```
require(PowerTOST)
    sampleN.TOST(alpha=0.05,
    targetpower=0.80, theta0=0.95,
    CV=0.30, design='2x2')
```

```
alpha    <- 0.05      # alpha
CV       <- 0.30      # intra-subject CV
theta1   <- 0.80      # lower acceptance limit
theta2   <- 1/theta1  # upper acceptance limit
theta0   <- 0.95      # expected ratio T/R
PwrNeed  <- 0.80      # minimum power
Limit    <- 1000      # Upper Limit for Search
n        <- 4         # start value of sample size search
s        <- sqrt(2)*sqrt(log(CV^2+1))
repeat{
  t    <- qt(1-alpha,n-2)
  nc1  <- sqrt(n)*(log(theta0)-log(theta1))/s
  nc2  <- sqrt(n)*(log(theta0)-log(theta2))/s
  prob1 <- pt(+t,n-2,nc1); prob2 <- pt(-t,n-2,nc2)
  power <- prob2-prob1
  n    <- n+2        # increment sample size
  if(power >= PwrNeed | (n-2) >= Limit) break }
Total    <- n-2
if(Total == Limit){
  cat('Search stopped at Limit', Limit,
      ' obtained Power', power*100, '%\n')
  } else
  cat('Sample Size', Total, '(Power', power*100, '%)\n')
```

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Which Power?

- Generally Producer's Risk 10–20%
  - Plan for 90% – allowing for contingency *e.g.*,
    - drop-outs,
    - CV_{intra} higher than assumed,
    - deviation of test from reference larger than expected.
  - Power $>$90% might lead to ethical problems ('forced bioequivalence').
  - FDA (2001):   80–90%
  - EMA (2010):   'appropriate'…
  - Russia (2008, 2011 draft): ≥80%

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End of the Story?

- *'Doing the maths'* is just *part* of the job!
  - Does it make sense to rely on studies of different origin and sometimes unknown quality?
    - The reference product may have been subjected to many *(minor only?)* changes from the formulation used in early publications.
    - Different bioanalytical methods are applied. Newer (*e.g.* LC/MS-MS) methods are not *necessarily* better in terms of variability.
    - Generally insufficient information about the clinical setup (*e.g.*, posture control).
    - Review studies critically; don't try to mix oil with water.

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Sensitivity Analysis

- ICH E9 (1998)
  - Section 3.5 Sample Size, paragraph 3
    - The method by which the sample size is calculated should be given in the protocol […]. The basis of these estimates should also be given.
    - It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions.
    - In confirmatory trials, assumptions should normally be based on published data or on the results of earlier trials.

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Sensitivity Analysis

- Example

  nQuery Advisor: $\sigma_w = \sqrt{\ln(CV_{intra}^2 + 1)}; \sqrt{\ln(0.2^2 + 1)} = 0.198042$

nQuery Advisor - [MTE2co-1.nqa]

File Edit View Options Assistants Randomize Plot Window Help

t-tests (TOST) of equivalence in ratio of means for crossover design (natural log scale)

	90% power	25% CV	4 drop outs	25% CV + d.o.	PE 90%	worst case
Test significance levels, α (one-sided)	0.050	0.050	0.050	0.050	0.050	0.050
Lower equivalence limit for μ_T / μ_S, Δ_L	0.800	0.800	0.800	0.800	0.800	0.800
Upper equivalence limit for μ_T / μ_S, Δ_U	1.250	1.250	1.250	1.250	1.250	1.250
Expected ratio, μ_T / μ_S	0.950	0.950	0.950	0.950	0.900	0.900
Crossover ANOVA, sqrt(MSE) (ln scale)	0.198042	0.246221	0.198042	0.246221	0.198042	0.246221
SD differences, σ_d (ln scale)	0.280074	0.348209	0.280074	0.348209	0.280074	0.348209
Power (%)	90.00	77.60	86.88	69.53	66.94	45.09
n per sequence group	13	13	11	11	13	11

20% CV:
n=26

25% CV:
power 90% → **78%**

20% CV, 4 drop outs:
power 90% → **87%**

25% CV, 4 drop outs:
power 90% → **70%**

20% CV, PE 90%:
power 90% → **67%**

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Sensitivity Analysis

- Example

PowerTOST, function *sampleN.TOST*

```
require(PowerTOST)
sampleN.TOST(alpha=0.05, targetpower=0.9, theta0=0.95,
             theta1=0.8, theta2=1.25, CV=0.2, design='2x2')

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

alpha = 0.05, target power = 0.9
BE margins          = 0.8 ... 1.25
Null (true) ratio = 0.95,   CV = 0.2
Sample size
 n      power
26    0.917633
```

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Sensitivity Analysis

- To estimate Power for a given sample size, use function *power.TOST*

```
require(PowerTOST)
power.TOST(theta0=0.95, CV=0.25, n=26)
[1] 0.7760553

power.TOST(theta0=0.95, CV=0.20, n=22)
[1] 0.8688866

power.TOST(theta0=0.95, CV=0.25, n=22)
[1] 0.6953401

power.TOST(theta0=0.90, CV=0.20, n=26)
[1] 0.6694514

power.TOST(theta0=0.90, CV=0.25, n=22)
[1] 0.4509864
```
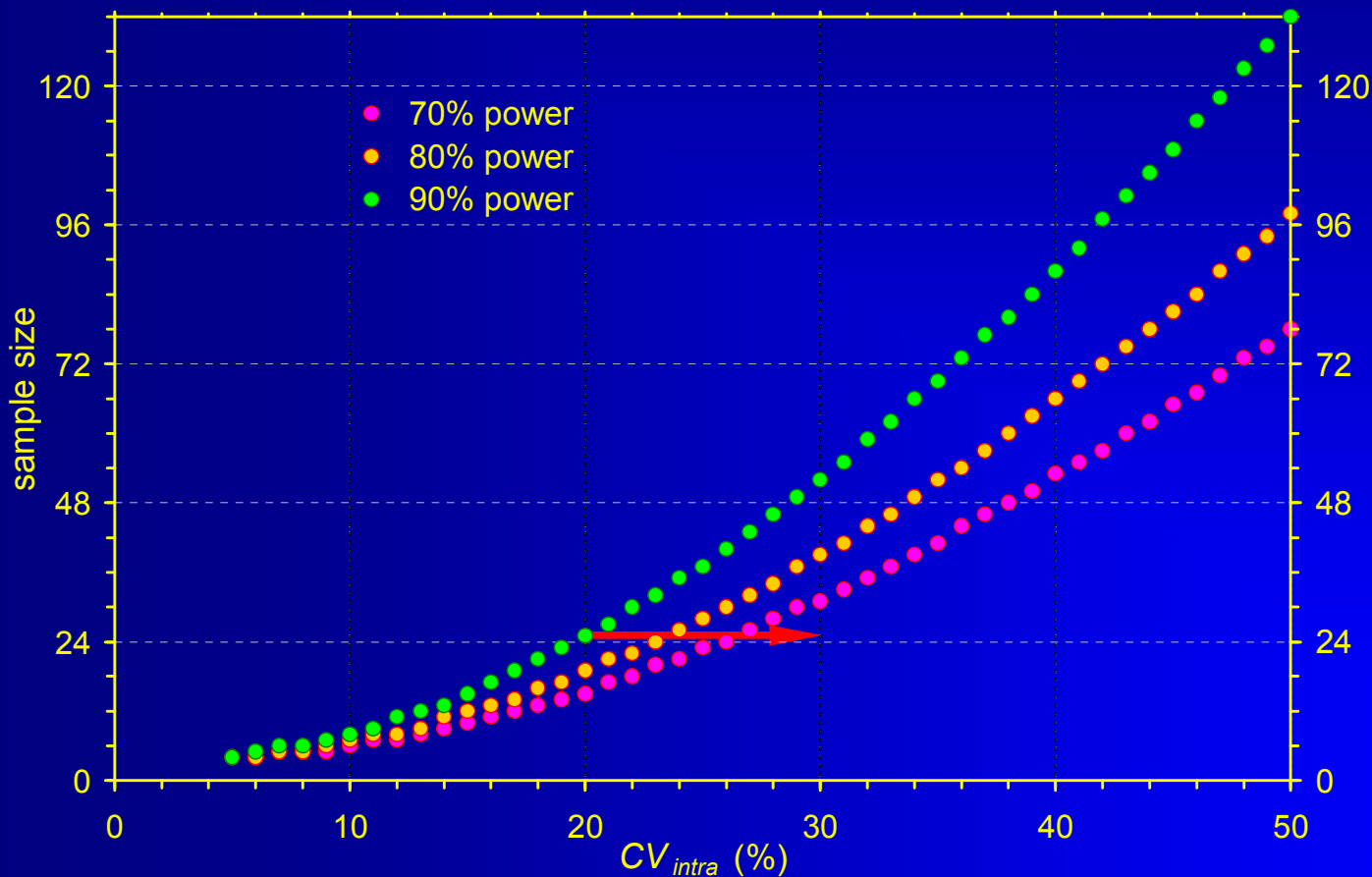
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CV based on assumptions!

2×2 cross-over, T/R 0.95

Legend:
- 70% power
- 80% power
- 90% power

y-axis: sample size

x-axis: CV_{intra} (%)

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

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

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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.

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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)

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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

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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, Dexametha-
   sone / Tobramycin.

- EMA (Jan 2010)

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

- Russia (Draft 2011)

   Acceptable (Methods B and C).

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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.

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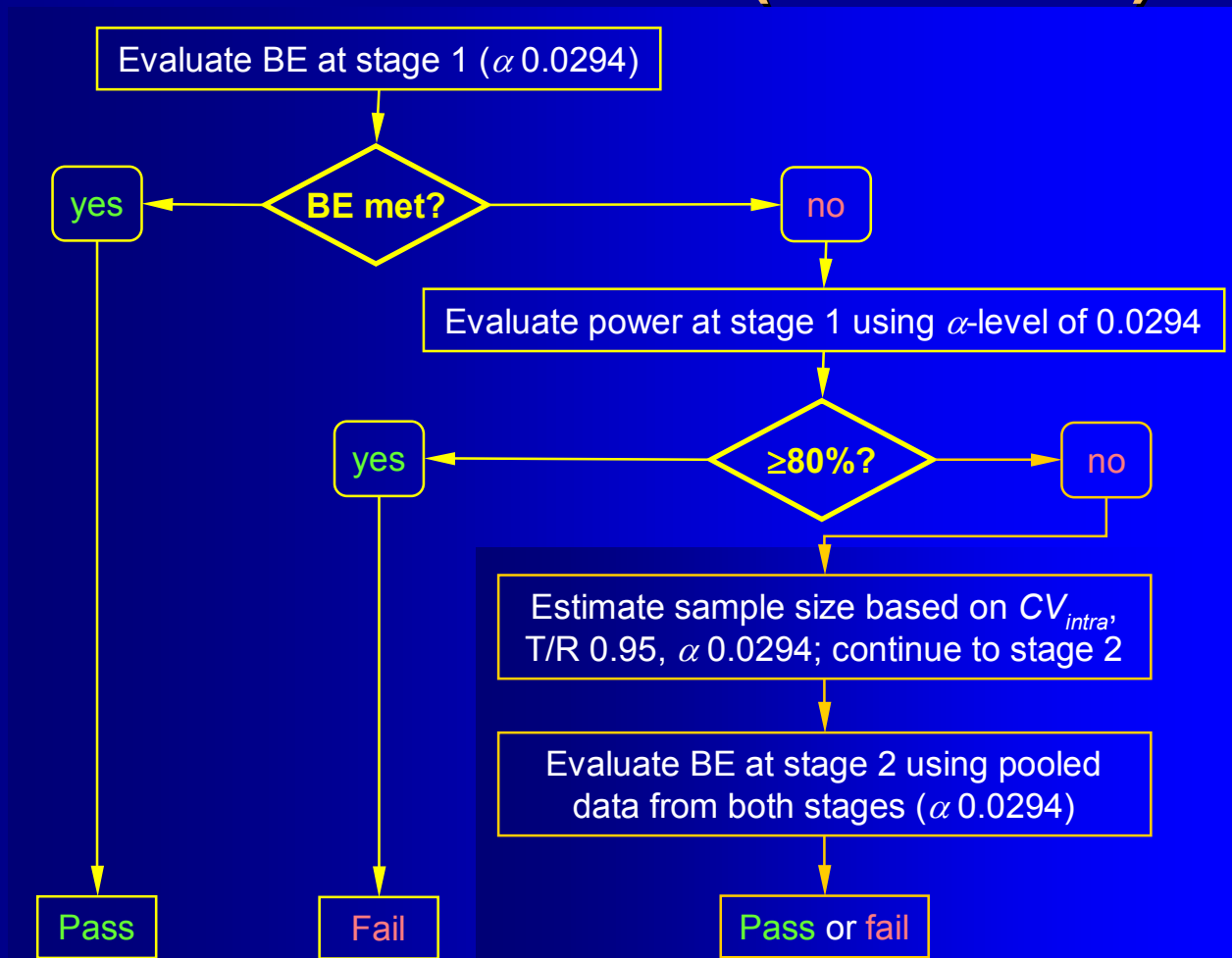
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Two-Stage Design

- 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 alternatives and the choice of how much alpha to spend at the interim analysis is at the company's discretion.

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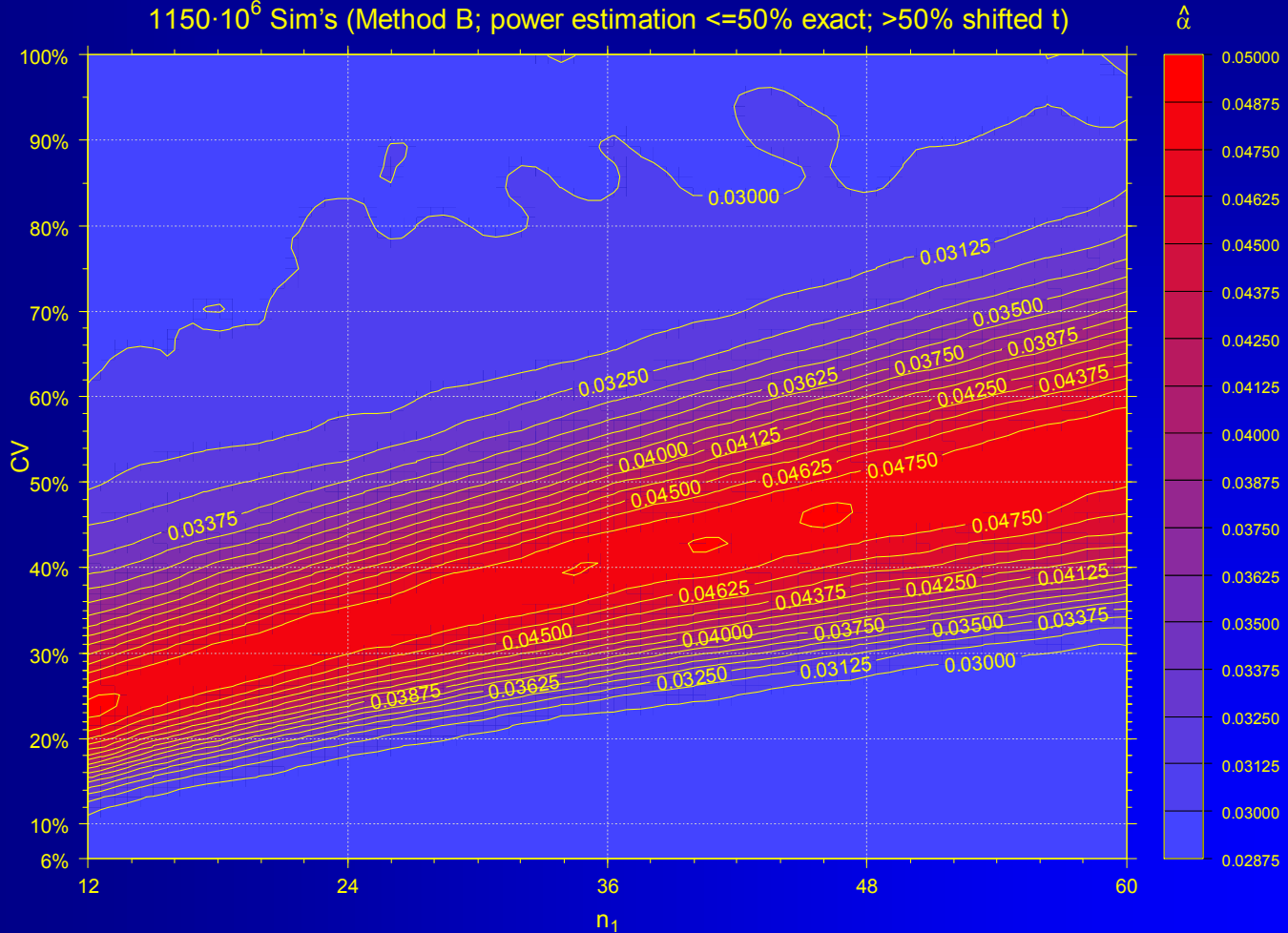
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Two-Stage Design

- 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.
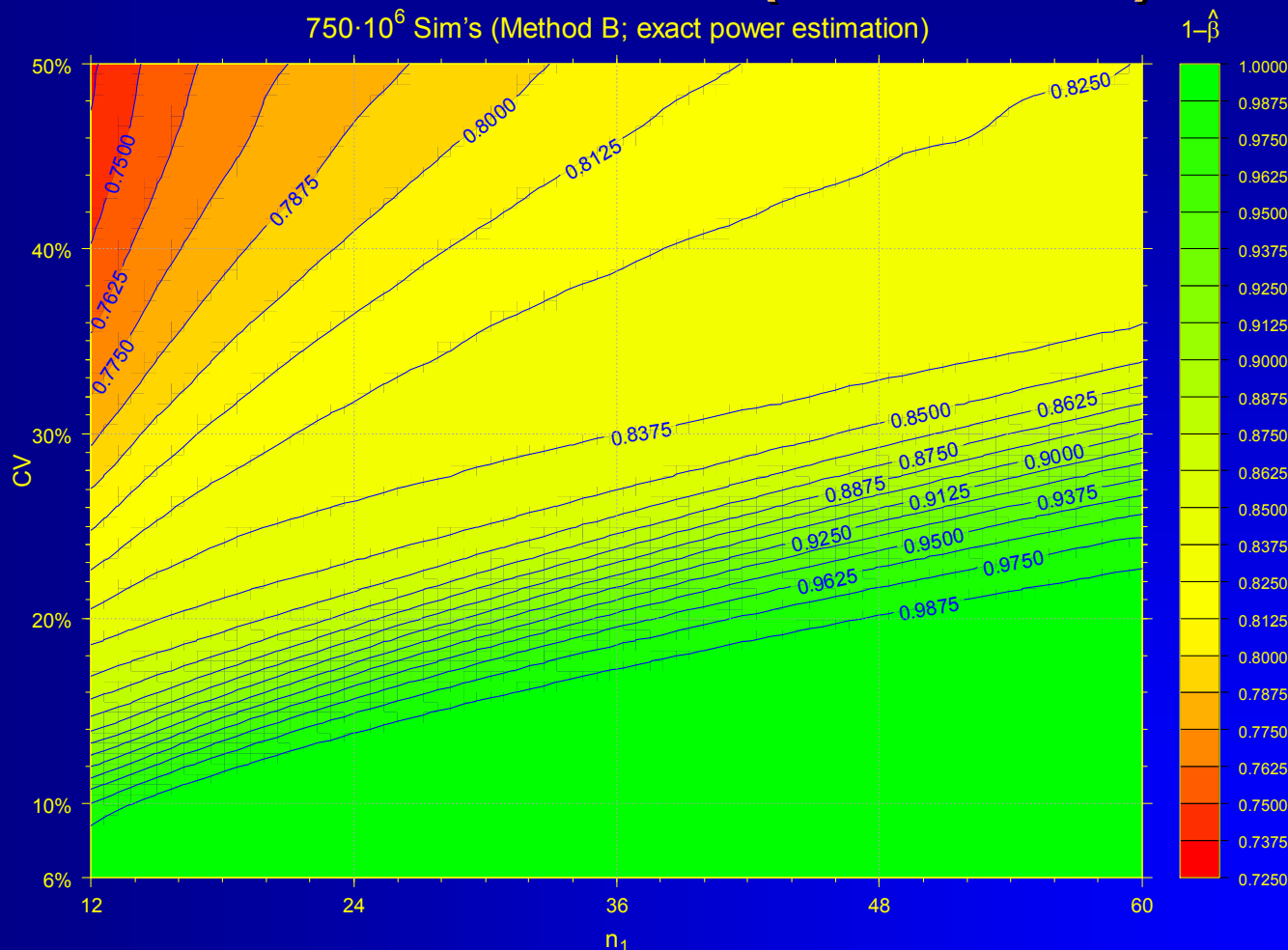
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Potvin *et al.* (Method B)

Evaluate BE at stage 1 (α 0.0294)

BE met?

yes → Pass

no → Evaluate power at stage 1 using α-level of 0.0294

≥80%?

yes → Fail

no →

Estimate sample size based on CV_{intra}, T/R 0.95, α 0.0294; continue to stage 2

Evaluate BE at stage 2 using pooled data from both stages (α 0.0294)

Pass or fail

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Potvin *et al.* (Method B)

1150·10^6 Sim's (Method B; power estimation <=50% exact; >50% shifted t)

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Potvin *et al.* (Method B)

$750 \cdot 10^6$ Sim's (Method B; exact power estimation)

$1-\hat{\beta}$

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Potvin *et al.* (Method B)

750·10⁶ Sim's (Method B; exact power estimation)

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Potvin *et al.* (Method B)

Sample size penalty (*CV* 14–40%, 80% power)

- planned for 0.0500
- planned for 0.0294

$n_{total} = 1.084n$

$n_{total} = 1.023n$

n_{total}: average sample size (two-stage)

n: sample size (fixed)

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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).

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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 $1 - 2 \times \alpha = 94.12\%$ CI is calculated.
  - Overall patient's risk preserved at ≤ 0.05.

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Potvin *et al.* (Method B)

- Technical Aspects (cont'd)
  - If the study is stopped after stage 1, the (conventional) statistical model is:
    ```
    fixed:  sequence + period + treatment
    random: subject(sequence)
    ```
  - If the study continues to stage 2, the model for the combined analysis is:
    ```
    fixed:  sequence + stage + period(stage) + treatment
    random: subject(sequence × stage)
    ```
  - No poolability criterion!
    Combining is *always allowed* – even if a significant difference between stages is observed. No need to test this effect.

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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%

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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
```

12 subjects in stage 1, conventional BE model

CV_{intra} 18.2%

```
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.
```

α 0.0294

Failed with 94.12% Confidence Interval

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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

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
```

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

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

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Potvin *et al.* (Method B)

```
Model Specification and User Settings
     Dependent variable : Cmax (ng/mL)
               Transform : LN
             Fixed terms : int+Sequence+Stage+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.
```
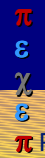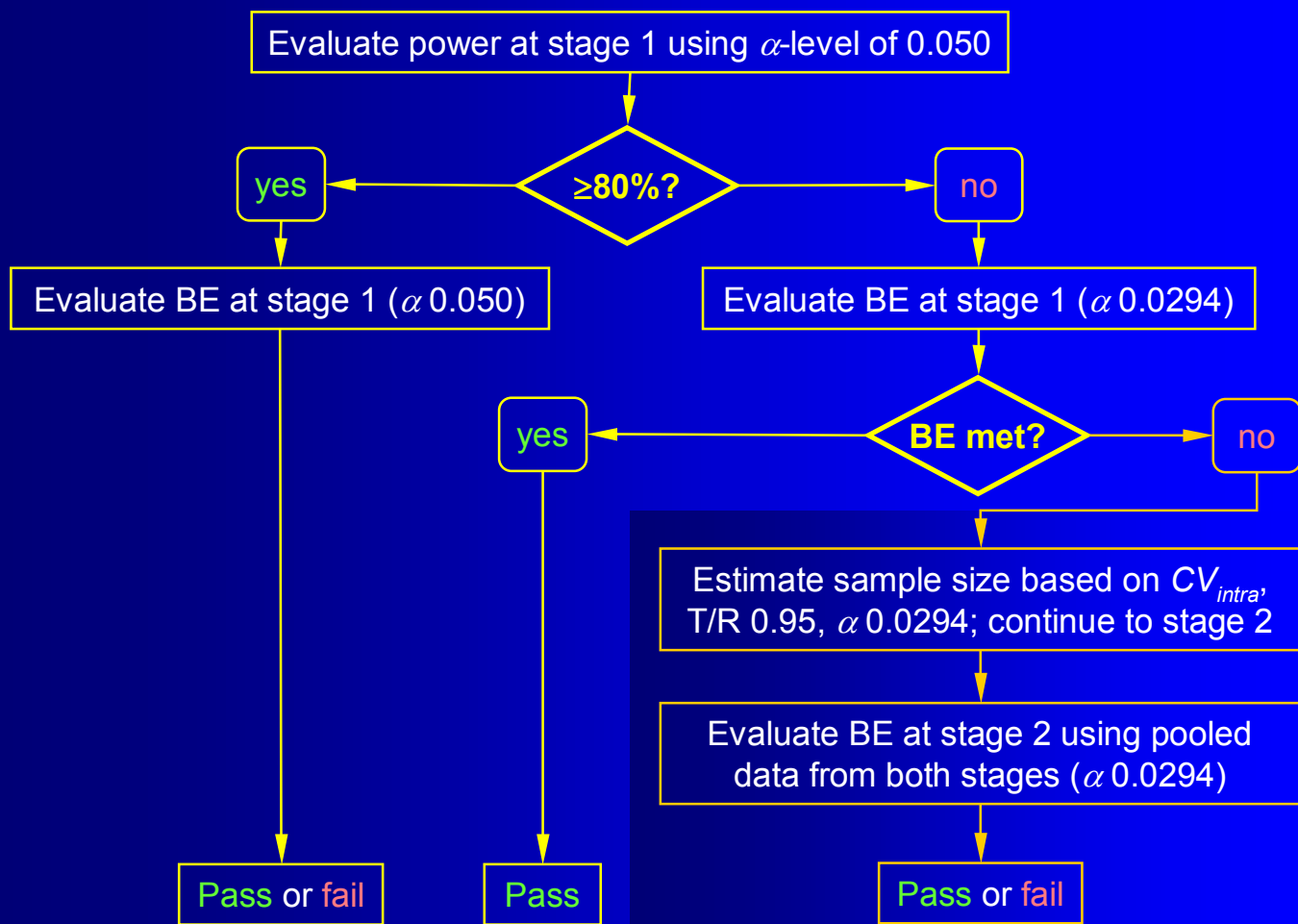
8 subjects in stage 2 (20 total), modified model in pooled analysis

α 0.0294 in pooled analysis

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

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Potvin *et al.* (Method C)

Evaluate power at stage 1 using α-level of 0.050

$\geq$**80%?**

yes → Evaluate BE at stage 1 (α 0.050)

no → Evaluate BE at stage 1 (α 0.0294)

BE met?

yes

no

Estimate sample size based on CV_{intra}, T/R 0.95, α 0.0294; continue to stage 2

Evaluate BE at stage 2 using pooled data from both stages (α 0.0294)

Pass or fail

Pass

Pass or fail

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Potvin *et al.* (Method C)

1150·10⁶ Sim's (Method C; power estimation – shifted t)

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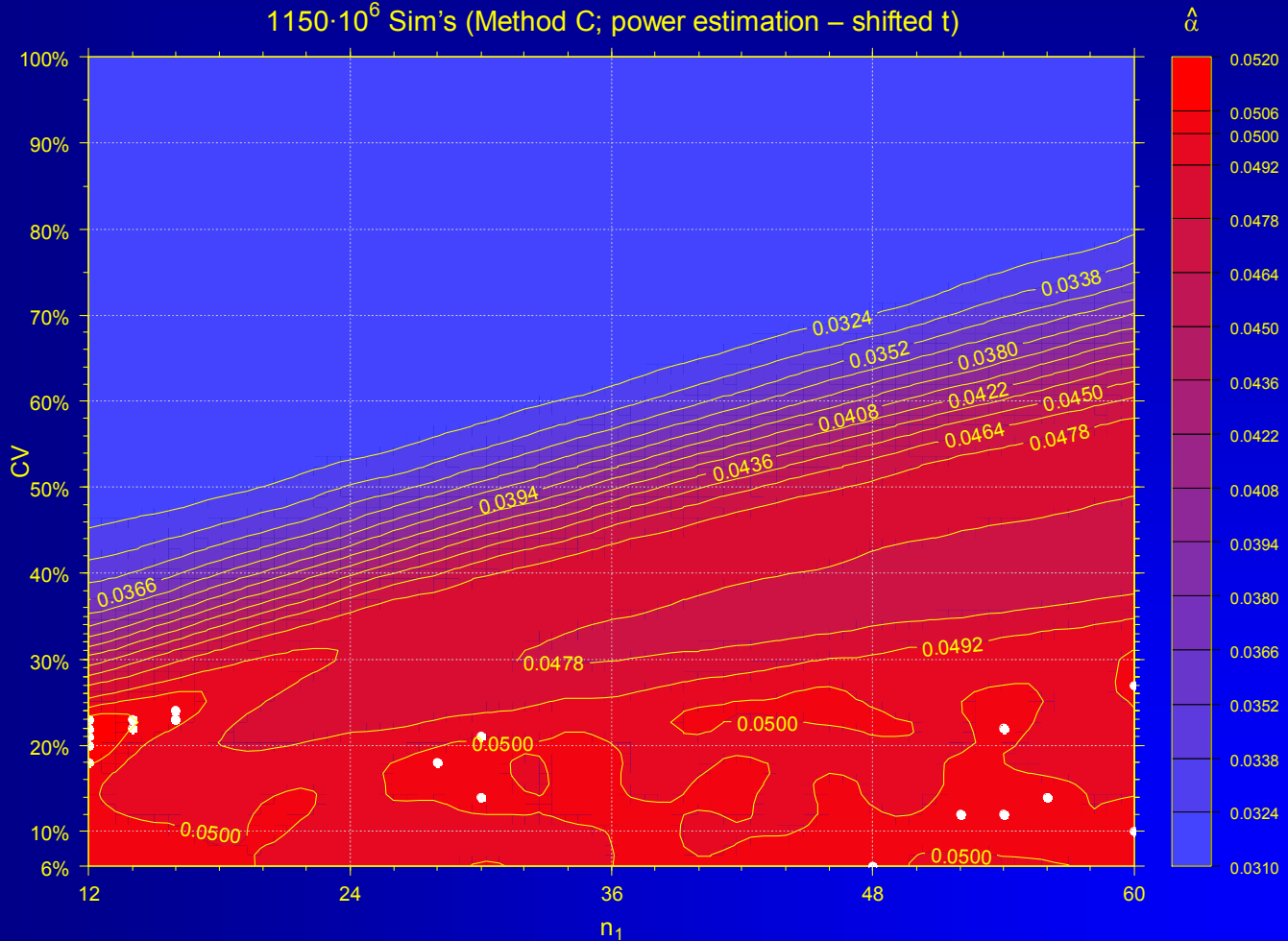
Potvin *et al.* (Method B *vs.* C)

- Pros & cons
  - Method C (*if power* $\geq 80\%!$) 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 reason-able 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.

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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.

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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)

$1150 \cdot 10^6$ Sim's (Method D; power estimation – shifted t)

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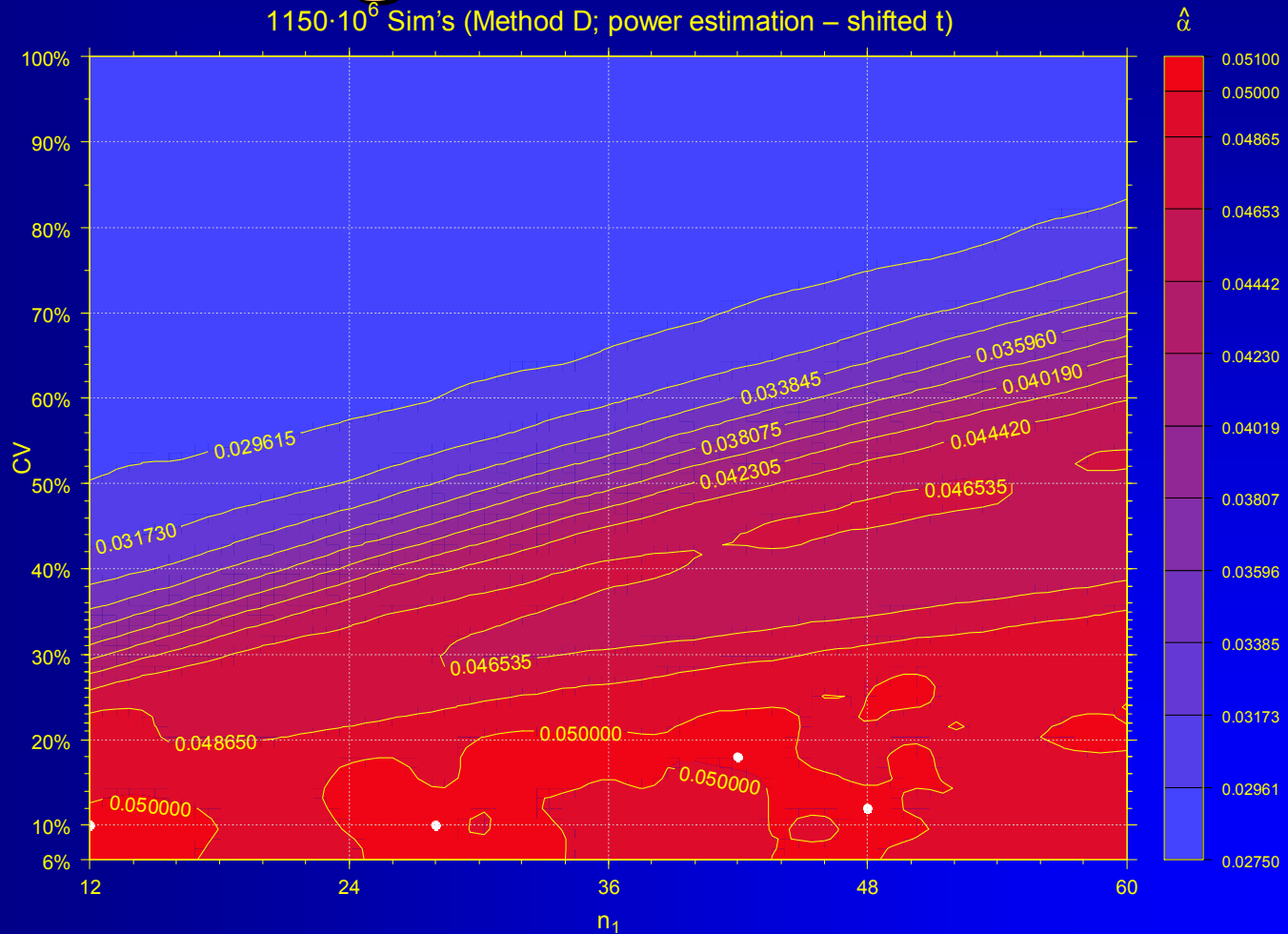
Case Studies (EMA)

- 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)

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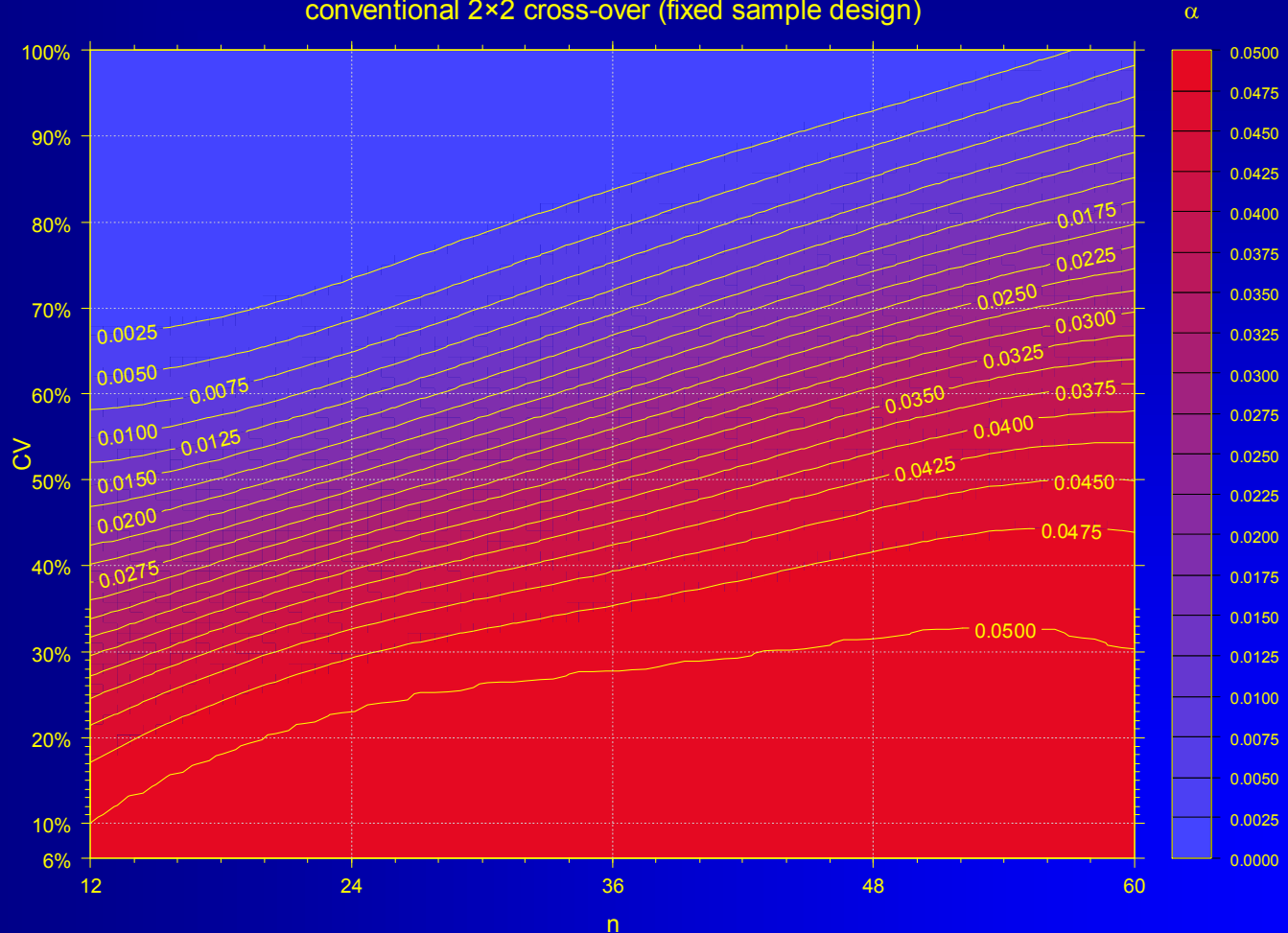
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Case Studies (EMA)

- 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…

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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).

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Don't panic!

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

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Thank You!
Two-Stage Designs
Open Questions?

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

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To bear in Remembrance...

Power. That which statisticians are always calculating but never have.

Power Calculation – A guess masquerading as mathematics.   *Stephen Senn*

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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