'Perfecting' the two stage study design

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Overview

- History / early approaches
  - Add-on studies
  - Problems with α-inflation
- Uncertain CV …
- Recent developments
  - Review of guidelines
  - Two-stage sequential designs

Overview

- Open issues
  - Feasibility / futility rules
  - Arbitrary PE and/or power; adaption for stage 1 PE
  - Dropping a candidate formulation from a higher-order X-over
  - Application to replicated designs (for HVDs/HVDPs)

History / early approaches

- Sometimes properly planned studies fail due to
  - Pure chance (producer's risk hit)
  - False assumptions about variability and/or T/R-ratio
  - Poor study conduct (increasing variability)
  - 'True' bioinequivalence
- The patient's risk must be preserved
  - Already noticed at Bio-International Conferences (1989, 1992) and guidelines from the 1990s

History / early approaches

- *'The primary concern in bioequivalence assessment is to limit the risk of erroneously accepting bioequivalence. Only statistical procedures which do not exceed the nominal risk of 5% can be approved, and among them the one with the smallest risk of erroneously rejecting bioequivalence should be selected.' **
- Performing a second study and pooling data with the first's not acceptable
- Performing a (much larger) second study and base BE on this study *alone* was (and is) acceptable

* **CPMP Working Party**
Investigation of Bioavailability and Bioequivalence: Note for Guidance
Section 3.6 Data analysis, Document Ref. III/54/89-EN (1 May 1992)

History / early approaches

- However, naïve pooling (*without* α-adjustment) was performed in the past
  - Statistical model modified in order to include a formulation-by-study interaction factor.
  - Test for homogeneity of error variances between studies
  - Pooling only acceptable if both tests not significant*

* **H Mellander**
Problems and Possibilities with the Add-On Subject Design, in:
Midha KK, Blume HH (eds.)
Bio-International. Bioavailability, Bioequivalence and Pharmacokinetics
medpharm Scientific Publishers, Stuttgart, pp. 85–90 (1993)

Add-on Designs

- Example (acc. to Canada's 1992+ guidances)
  - Second part in at least 12 subjects
    Pooling only allowed if both of two consistency tests not significant (p>0.05)
  - Equality of residual mean squares (F-test) of the two parts. Smaller MSE must be used as the denominator.
    Example:
    0.01321 (1st part: n=55, df 53)
    0.01718 (2nd part: n=14, df 12)

Add-on Designs

Sum of Squares

Hypothesis	DF	SSE	MSE	F_stat	P_value
Sequence	1	0.0271658	0.0271658	0.173639	0.6786
Sequence*Subject	53	8.29185	0.15645	11.844	<0.0001
Treatment	1	0.211196	0.211196	15.9885	0.0002
Period	1	0.0271536	0.0271536	2.05565	0.1575
Error	53	0.700088	0.0132092		

Sum of Squares

Hypothesis	DF	SSE	MSE	F_stat	P_value
Sequence	1	0.0489527	0.0489527	0.419204	0.5295
Sequence*Subject	12	1.4013	0.116775	6.79641	0.0012
Treatment	1	0.0349142	0.0349142	2.03203	0.1795
Period	1	0.0839476	0.0839476	4.88581	0.0472
Error	12	0.206183	0.0171819		

$$\hat{F} = \frac{MSE_{large}}{MSE_{small}} = \frac{0.0171819}{0.0132092} = 1.30075$$

$$F_{1-0.05,12,53} = 1.940$$

$$p\left(\hat{F}\right) = 0.24595 > 0.05$$ ✓

Add-on Designs

- Example (Canada cont'd)
  - Second part in at least 12 subjects. Pooling is only allowed if two consistency tests not significant (p>0.05):
    - Since first test not significant (p 0.246), pool studies
    - Now test for study-by-formulation interaction

Add-on Designs

```
Tests of Model Effects
           Hypothesis    Numer_DF    Denom_DF      F_stat     P_value
-------------------------------------------------------------------------
                  int           1        56.5   2144.16       <0.0001
                Study           1        56.5      0.0007      0.9784
            Treatment           1        64.6      9.9949      0.0024
      Treatment*Study           1        64.6      0.1156      0.7349

Bioequivalence Statistics

User-Specified Confidence Level for CI's = 95.0000
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: R   LSMean=    6.088010  SE=    0.132921  GeoLSM=  440.543718
-------------------------------------------------------------------------
Test:      T   LSMean=    6.167145  SE=    0.132921  GeoLSM=  476.822902

    Difference =      0.0791,  Diff_SE=    0.0250,  df= 64.6
    Ratio(%Ref) =   108.2351

    CI  90% = (  103.8061,  112.8531)
    CI  95% = (  102.9556,  113.7853)
    Average bioequivalence shown for confidence=95.00 and percent=20.0.
```

$$F_{1-0.05,1,64.6} = 3.989$$

$$p(0.1156) = 0.7349 > 0.05$$

Add-on Designs

- Example (Canada cont'd)
  - Formulation-by-study interaction not significant (p 0.7349), pooled analysis acceptable
  - No α–adjustment mentioned in 1992 guideline, but recommended in 2010 draft (Bonferroni: 95% CI)
  - 2010 draft allows also for group sequential designs
  - Group sequential designs allow better control of patient's risk

Problems with α-inflation

- Patient's risk likely is not preserved
  - The probability to obtain at least one significant result with k independent (!) t-tests (at level α) is

$$P(k) = 1 - (1 - \alpha)^k$$

$$P(2) = 1 - (1 - 0.05)^2 = 0.0975$$

    - Bonferroni-correction of two studies would mandate calculation of a 95% confidence interval

$$\alpha_{adj} = \alpha / k$$

$$P_{adj}(2) = 1 - (1 - 0.025)^2 = 0.04938 < 0.05$$

    - Applicability doubtful since no *independent* tests!

Problems with α-inflation

- Patient's risk (cont'd)
  - For two repeated tests on accumulating data the overall level is ~ 8%[1]
  - In naïve pooling the variance will be underestimated[2]
  - Simulations of BE studies (sample sizes 24 – 48, CV_{intra} 19 – 37%, 1 – 3 interim looks) showed empirical α of up to 5.97%[3]

1 **Armitage P, McPherson K, and BC Rowe**
Repeated significance tests on accumulating data
J R Statist Soc A 132, 235–44 (1969)

2 **Wittes J, Schabenberger O, Zucker D, Brittain E, and M Proschan**
Internal pilot studies I: type I error rate of the naïve t-test
Statistics in Medicine 18, 3481–91 (1999)

3 **Hauck WW, Preston PE, and FY Bois**
A group sequential approach to crossover trials for average bioequivalence
Journal of Biopharmaceutical Statistics 7(1), 87–96 (1997)

Problems with α-inflation

- Patient's risk (cont'd)
  - Simulations of 1 Mio BE studies (12 subjects in 1st study, CV_{intra} 20%, sample size re-estimation based on PE 0.95 and CV_{intra} of 1st study) showed empirical α of 5.84%[1]
  - With two repeated tests at 2.94% overall $\alpha \sim 5\%$[2]
  - Derived for tests assuming normally distributed data with known variances. Approximately valid if sample size not too small.

1 **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

2 **SJ Pocock**
Group sequential methods in the design and analysis of clinical trials
Biometrika 64, 191–9 (1977)

Uncertain CV …

- CV_{intra} used in sample size estimation is *not set in stone* but an *estimate*!
  - Sample sizes for 1–β 90%, PE 0.95, CV_{intra} 20% → n=26
  - Not done yet! What if $CV_{intra} \neq 20\%$?

CV_{intra}	n	$power_n$	$power_{n=26}$
15	16	0.92602	0.99153
16	18	0.92685	0.98379
17	20	0.92601	0.97253
18	22	0.92400	0.95763
19	24	0.92114	0.93922
20	**26**	0.91763	0.91763
21	28	0.91362	0.89329
22	30	0.90919	0.86659
23	32	0.90443	0.83794
24	36	0.91451	0.80767
25	38	0.90889	0.77606

Recent developments

- Review of guidelines
  - New Zealand (Oct 2001)
    - Sequential Designs
      - Declared in the protocol
      - Maximum sample size *a priori* (≤40!)
      - 'Appropriate statistical tests (e.g., sequential *t*-test)'
  - FDA
    - Sequential Designs: not mentioned in guidances but acceptable (pers. comm. Barbara Davit, Ljubljana, May 2010)
  - EMA (Jan 2010)
    - Sequential Designs: fairly detailed informations given

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.

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
    - stated in Canadian draft guidance (2010) and EMA's BE guideline (2010).

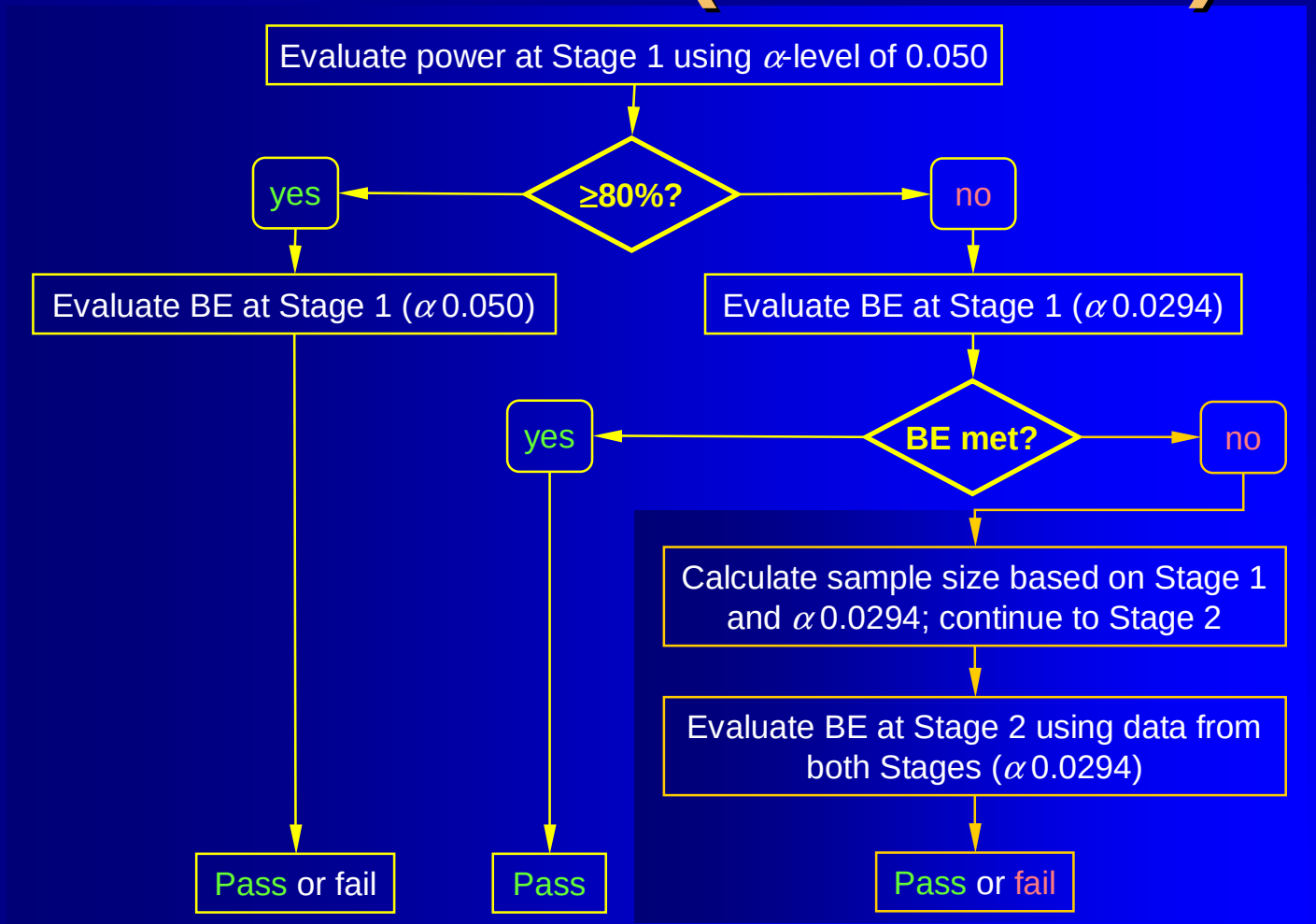
AL Gould
Group Sequential Extension of a Standard Bioequivalence Testing Procedure
J Pharmacokin Biopharm 23/1, 57–86 (1995)

Sequential Designs

- Methods by Potvin *et al.* (2008) promising
  - Supported by 'The Product Quality Research Institute' (members: FDA/CDER, Health Canada, USP, AAPS, PhRMA, …)
    - Acceptable by US-FDA
    - Canada? Or Gould (1995) mandatory?
    - Acceptable as a Two-Stage Design in the EU
    - Three of BEBAC's protocols already approved by German BfArM

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

Potvin *et al.* (Method C)



Potvin *et al.* (Method C)

- Technical Aspects
  - Only *one* Interim Analysis (after Stage 1)
  - If possible, use software (too wide step sizes in Diletti's tables), preferrable the exact method (avoid approximations)
  - Should be termed 'Power Analysis' *not* 'Bioequivalence Assessment' in the protocol
  - No *a-posteriori* Power – only a validated method in the decision tree
  - No adjustment for the PE observed in Stage 1

Potvin *et al.* (Method C)

- Technical Aspects (cont'd)
  - No stop criterion (*'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)
  - If power <80% in Stage 1 or in the pooled analysis (data from Stages 1 + 2), Pocock's α 0.0294 is used (*i.e.*, the $1 - 2\times\alpha = 94.12\%$ CI is calculated)
  - Overall patient's risk preserved at ~≤0.05

Potvin *et al.* (Method C)

- 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)
```

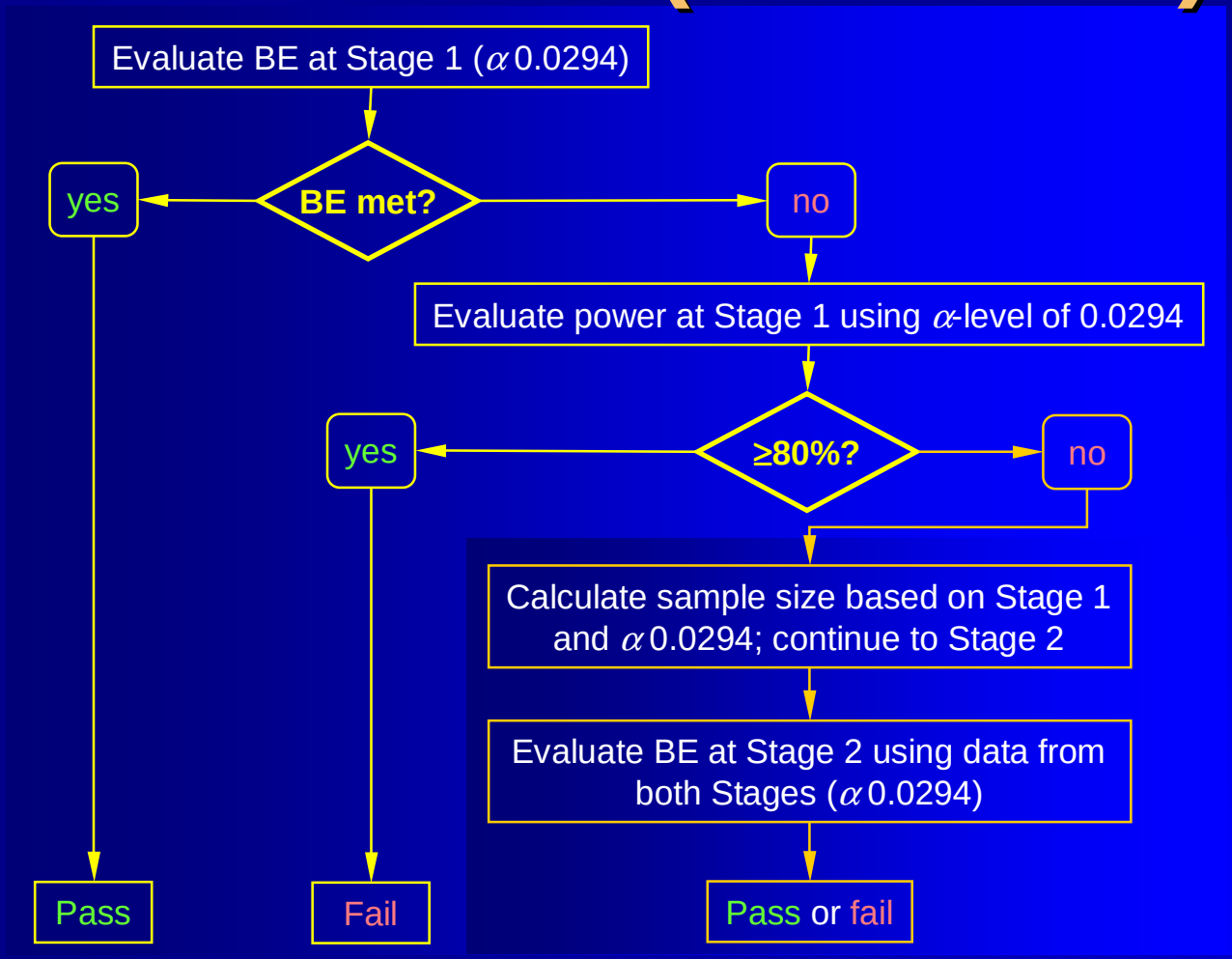
  - No poolability criterion; combining is *always allowed* – even for significant differences between Stages

Potvin *et al.* (Method C)

- Technical Aspects (cont'd)
  - Potvin *et al.* used a simple approximative power estimation based on the shifted *t*-distribution (to increase speed in their simulations?)
  - If possible use the exact method (Owen; package *PowerTOST* exact = TRUE) or at least the one based on the noncentral *t*-distribution (*PowerTOST* exact = FALSE)
  - Power obtained in Stage 1:

method	power
approx. (shifted *t*)	64.94%
approx. (noncentral *t*)	66.45%
exact	66.47%

Potvin *et al.* (Method B)



Potvin *et al.* (example B/C)

```
Model Specification and User Settings
      Dependent variable : Response
               Transform : LN
           Fixed terms : int+Sequence+Treatment+Period
    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  90% = (   95.1474,  124.3162)
    CI User = (   92.9291,  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 (if power <80%)

Failed 90% CI (if power ≥80%) and 94.12% CI (if power <80%)

Potvin *et al.* (example B/C)

```
require(PowerTOST)
power.TOST(alpha=0.05, logscale=TRUE,
           theta1=0.8, theta2=1.25, theta0=0.95,
           CV=0.182132, n=12,
           design = "2x2", exact = TRUE)

[1] 0.6646934
```

α 0.05 (C), α 0.0294 (B), expected ratio 95% – *not* 108.76% obs. in stage 1! CV_{intra} 18.2%, 12 subjects in Stage 1

Power 66.5% – 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", exact = TRUE,
             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
```

Calculate total sample size: expected ratio 95%, CV_{intra} 18.2%, 80% power

Total sample size 20: include another 8 for Stage 2

Potvin *et al.* (example B/C)

```
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 for pooled analysis

α 0.0294 in pooled analysis

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

Potvin *et al.* (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 goes 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

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

- Recommendations
  - Method C preferred due to slightly higher power than method B
  - 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 (94.12% CI) or stage 2 as the 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 ~20% higher.

Sequential Designs

- Methods by Potvin *et al.* (2008) limited to point estimate of 0.95 and 80% power
  - Follow-up paper
    - Slight inflation of patient's risk (α 0.0547) observed in Methods B/C if PE 0.90 instead of 0.95 was used
    - Method D (like C, but α 0.0280 instead of α 0.0294)
    - Might be usefull if PE 0.95 and power 90% as well; *not validated yet!*

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. (2011), DOI: 10.1002/pst.483

Sequential Designs

- Caveats
  - Methods for 'classical' group-sequential designs derived based on
    - Test for differences (superiority, parallel groups)
    - Large samples (Z test of normal distributed data with known variance)
    - Fixed total sample size (interim analysis at N/k)
    - Balanced case (no drop outs)
  - Don't apply any published procedure unquestioned (*i.e.*, if not validated for bioequivalence)
  - *Simulations mandatory* to derive an empirical α ($\leq$0.052)!

Open Issues

- Feasibility / futility rules
  - It would be desirable to stop a study after stage 1 under certain circumstances
    - (1) BE is unlikely to be shown in even very high sample sizes (*e.g.*, CI outside acceptance range)
      → reformulate
    - (2) It turns out that the drug/formulation is highly variable
      → replicate design study in order to perform scaling required
    - (3) The calculated sample size exceeds the budget of the project by far

Open Issues

- Feasibility / futility rules
  - These points are not covered by Potvin *et al.*
  - If you decide to include a rule for early stopping, it's not part of the statistical procedure any more
  - (1) and (2) are ethically justifiable
  - (3) Acceptance?

Open Issues

- Arbitrary PE and/or power
  - Simulations mandatory
    - Set desired PE and power
    - Define maximum α-inflation (≤0.052?)
    - Simulate sufficiently large number of studies (N)
      - Count number of studies accepted BE at 1.25 (n_1) and number of studies rejected BE at the desired PE (n_2)
      - Empirical $\alpha = n_1/N$
      - Empirical $\beta = n_2/N$; power = $1 - \beta$
    - Start with Pocock's nominal α 0.0294 and decrease stepwise if empirical α too high
    - Compiled language almost necessary (speed!)

Open Issues

- Adaption for stage 1 PE (full adaptive design)
  - If applied naïvely, α-inflation of up to 30%!*
  - Various methods for superiority trials, but nothing in the area of BE published
  - Simulations mandatory

* **Cui L, Hung MJ, and S-J Wang**
Modification of sample size in group sequential clinical trials
Biometrics 55, 853–7 (1999)

Open Issues

- Dropping a candidate formulation from a higher-order cross-over design

Stage 1		
I	II	III
T_1	T_2	R
T_2	R	T_1
R	T_1	T_2
T_1	R	T_2
T_2	T_1	R
R	T_2	T_1
...	...	...

Stage 2	
I	II
R	T_2
T_2	R
...	...

How to decide *which* formulation to drop?

- Statistical model of BE assumes IID (common σ^2)
  - Let's assume to continue with T_2
  - If $\sigma^2_{T_1} > \sigma^2_{T_2}$ and/or σ^2_R, the pooled variance in Stage 1 will be inflated. The estimated total sample size will be too high. Expensive, but no influence on α expected.
  - If $\sigma^2_{T_1} < \sigma^2_{T_2}$ and/or σ^2_R, power will be lower – increasing the producer's risk only.

Don't try this at home!

- 6×3 dose proportionality study
  R 20 mg, T_1 30 mg, T_2 40 mg; CV_{intra} 8.76%
  - T_2÷2, all effects fixed (EMA), Method D_B, PE 90%, α 0.028

Stage 1					
I		II		III	
R	162.28	T_2	153.44	T_1	235.62
T_1	75.34	R	72.04	T_2	43.82
T_2	64.38	T_1	78.18	R	71.28
T_1	124.06	T_2	49.06	R	86.42
T_2	100.22	R	97.72	T_1	121.36
R	32.30	T_1	63.87	T_2	70.33
T_1	118.74	R	42.25	T_2	65.97
T_2	66.07	T_1	69.52	R	38.30

Stage 2			
I		II	
R	80.23	T_2	64.26
T_2	65.72	R	67.91
T_2	19.61	R	20.81
R	32.55	T_2	29.35

Extremely imbalanced due to arbitrary cut of original dataset! N=6 (single balanced block) would have zero df for sequences.

Don't try this at home!

```
Model Specification and User Settings
      Dependent variable : Response
               Transform : LN
           Fixed terms : int+sequence+treatment+period+subject(sequence)

Final variance parameter estimates:
          Var(Residual)   0.0811756

Bioequivalence Statistics
User-Specified Confidence Level for CI's = 94.4000
Percent of Reference to Detect for 2-1 Tests = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250
Reference: Reference   LSMean=  4.263887  SE=  0.103103  GeoLSM=  71.085745
-----------------------------------------------------------------------------
Test:      Test 1      LSMean=  4.686177  SE=  0.103103  GeoLSM= 108.437840
    Difference =      0.4223,  Diff_SE=    0.1436,  df= 12.0
    Ratio(%Ref) =   152.5451
    CI User = (112.5795, 206.6985)
    Failed to show average bioequivalence for confidence=94.40 and percent=20.0.
-----------------------------------------------------------------------------
Test:      Test 2      LSMean=  4.318248  SE=  0.103103  GeoLSM=  75.056997
    Difference =      0.0544,  Diff_SE=    0.1436,  df= 12.0
    Ratio(%Ref) =   105.5866
    CI User = ( 77.9237, 143.0697)
    Failed to show average bioequivalence for confidence=94.40 and percent=20.0.
```

8 subjects in Stage 1, all effects fixed (EMA)

CV_{intra} 8.13%

α 0.028 (Method B/D)

Don't try this at home!

```
require(PowerTOST)
power.TOST(alpha=0.0280, logscale=TRUE,
           theta1=0.8, theta2=1.25, theta0=0.90,
           CV=se2CV(0.0811756), n=8,
           design="3x6x3", exact=TRUE)

[1] 0.7776753

sampleN.TOST(alpha=0.0280, targetpower=0.80, logscale=TRUE,
             theta1=0.8, theta2=1.25, theta0=0.90,
             CV=se2CV(0.0811756), design="3x6x3", exact=TRUE,
             print=TRUE)

++++++++++++ Equivalence test - TOST ++++++++++++
             Sample size estimation
-----------------------------------------------
Study design:  3x6x3 crossover
log-transformed data (multiplicative model)

alpha = 0.0294, target power = 0.8
BE margins        = 0.8 ... 1.25
Null (true) ratio = 0.9,  CV = 0.08130951

Sample size
 n     power
12   0.930078
```

α 0.028, expected ratio 90%, MSE 0.08118 (CV_{intra} 8.13%), 8 subjects in Stage 1, 6×3 design

Power 77.8% <80% – initiate Stage 2

Calculate total sample size: expected ratio 90%, CV_{intra} 8.13%, 80% power, keeping 6×3 design

Total sample size 12: include another 4 for Stage 2

Don't try this at home!

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

Final variance parameter estimates:
           Var(Residual)     0.0985763

Bioequivalence Statistics
User-Specified Confidence Level for CI's = 94.4000
Percent of Reference to Detect for 2-1 Tests = 20.0%
A.H.Lower =  0.800   A.H.Upper =  1.250
Reference: Reference   LSMean=  3.888945  SE=  0.216489  GeoLSM=  48.859311
---------------------------------------------------------------------------
Test:      Test 1      LSMean=  4.284496  SE=  0.229396  GeoLSM=  72.565947
    Difference =      0.3956,  Diff_SE=    0.1256,  df= 14.825
    Ratio(%Ref) =   148.5202
    CI User = (114.4688, 192.7011)
    Failed to show average bioequivalence for confidence=94.40 and percent=20.0.
---------------------------------------------------------------------------
Test:      Test 2      LSMean=  3.889827  SE=  0.216489  GeoLSM=  48.902424
    Difference =      0.0009,  Diff_SE=    0.1069,  df= 14.825
    Ratio(%Ref) =   100.0882
    CI User = ( 80.1937, 124.9182)
    Average bioequivalence shown for confidence=94.40 and percent=20.0.
```

4 subjects in Stage 2 (12 total), modified model for pooled analysis

Don't try this at home!

- Lessons learned, open questions
  - Not validated! Don't think about using it at all!
  - Note that due to the massive imbalance the LSM of Test 1 (although not included in Stage 2) changed from Stage 1 in the pooled analysis!
    - Stage 1: 108.44
    - Pooled: 72.57
  - Drug has low CV_{intra}, but high CV_{inter} – Apples and oranges?

CV%	T_1	T_2	R	model
Stage 1	28.61	41.30	70.66	period
Stage 2	–	82.50	85.95	period
Pooled	28.61	56.91	65.87	period

Don't try this at home!

- Lessons learned, open questions
  - Must use software in the power calculation which can handle the degrees of freedom of a Williams' design in Stage 1 correctly (*e.g.*, *PowerTOST*)
  - Obvious which formulation to drop in this example, but what if formulations are similar in PEs? Keep the one with smaller CV_{inter}?
  - Design in the sample size estimation of Stage 2?
    - ~~2×2 (block size 2 → 10)~~
    - 3×6 (block size 6 → 12) ✓
    - The former would have failed in the example

Don't try this at home!

- Lessons learned, open questions
  - Tempting idea, but not recommended
    - until a statistical decision tree is developed and
    - suitable simulations have shown that the patient's risk is not inflated

Open Issues

- Replicated designs (HVDs/HVDPs)
  - Nothing published!
  - Statistical model?
  - Although EMA assumes equal variances of formulations (Q&A document Jan 2010) that does not reflect the 'real world' (quite often $\sigma^2_{WR} > \sigma^2_{WT}$)
  - If you set up simulations allow for different variances of test and reference

Congratulations!
Perfecting (?) the two stage study design
Open Questions?

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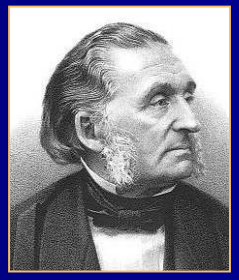
To bear in Remembrance...

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

Power: That which is wielded by the priesthood of clinical trials, the statisticians, and a stick which they use to beta their colleagues.

Power Calculation – A guess masquerading as mathematics.

Stephen Senn



You should treat as many patients as possible with the new drugs while they still have the power to heal.

Armand Trousseau