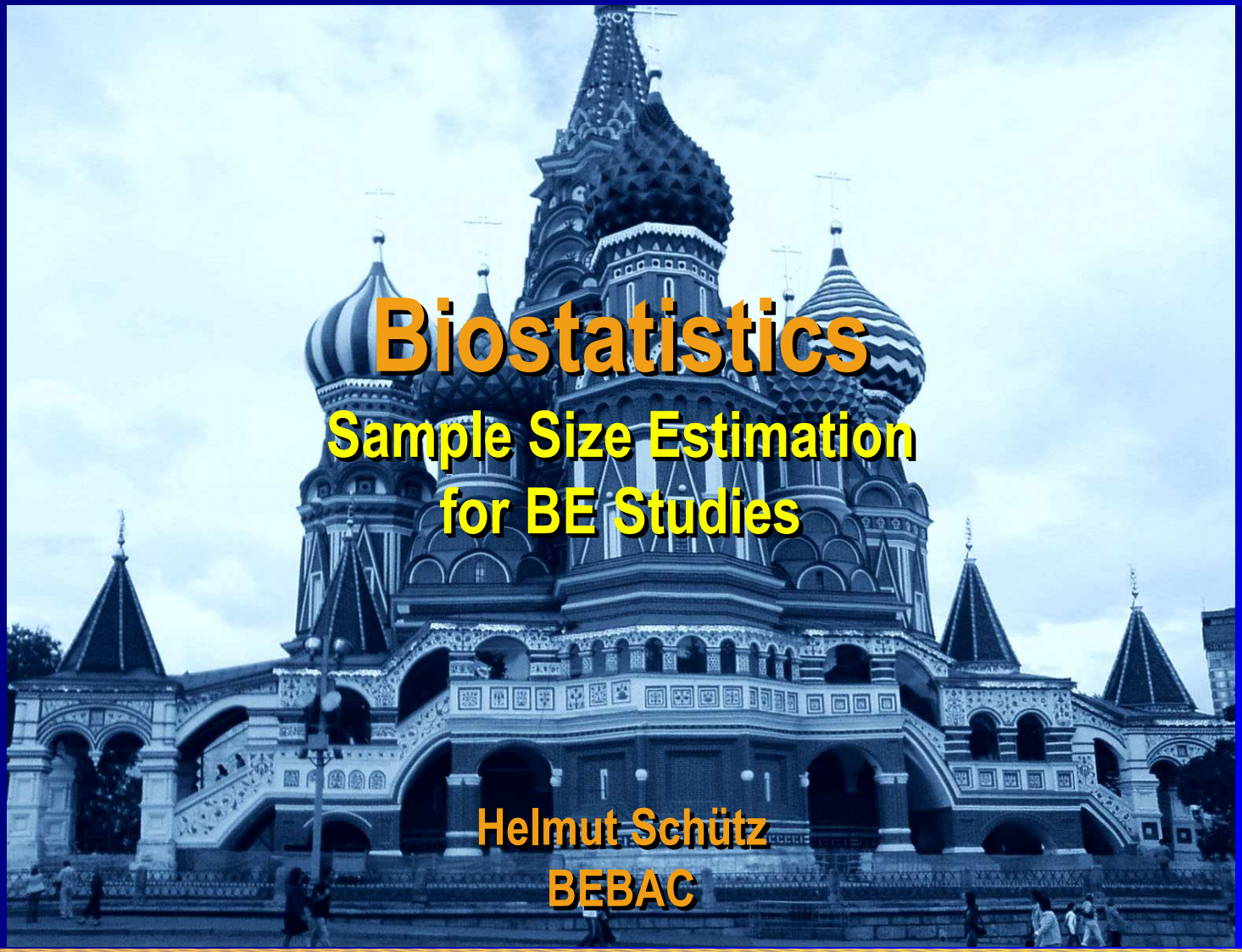


Biostatistics

Sample Size Estimation for BE Studies

Helmut Schütz
BEBAC

Overview

- ‘Classical’ sample size estimation in BE
  - Patient’s & producer’s risk
  - Power in study planning
- Uncertainties
  - Variability
  - Test/Reference-ratio
  - Sensitivity analysis
- Recent developments
  - Review of guidelines

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

α and β

- Or in more statistical terms:

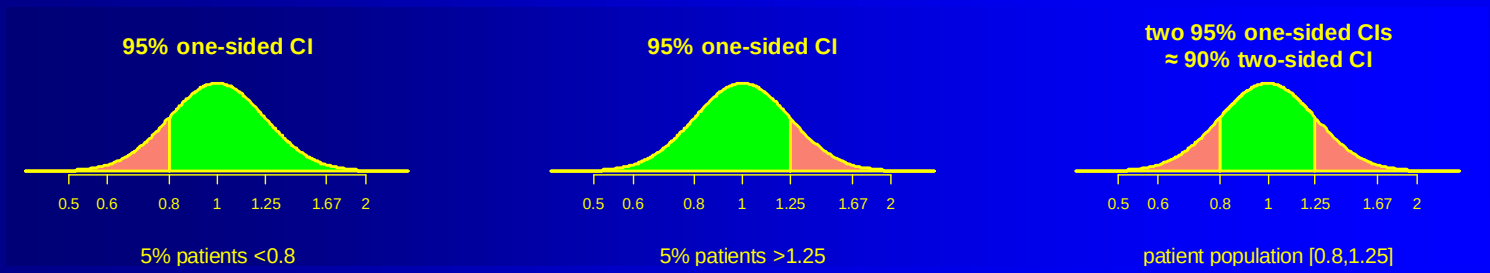
Decision	Null hypothesis true	Null hypothesis false
Null hypothesis rejected	Error type I	Correct (H_a)
Failed to reject null hypothesis	Correct (H_0)	Error type II

- In BE-testing the null hypothesis is bioinequivalence ($\mu_1 \neq \mu_2$)!

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

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.



… and β

- **Producer's Risk** to get no approval of an **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

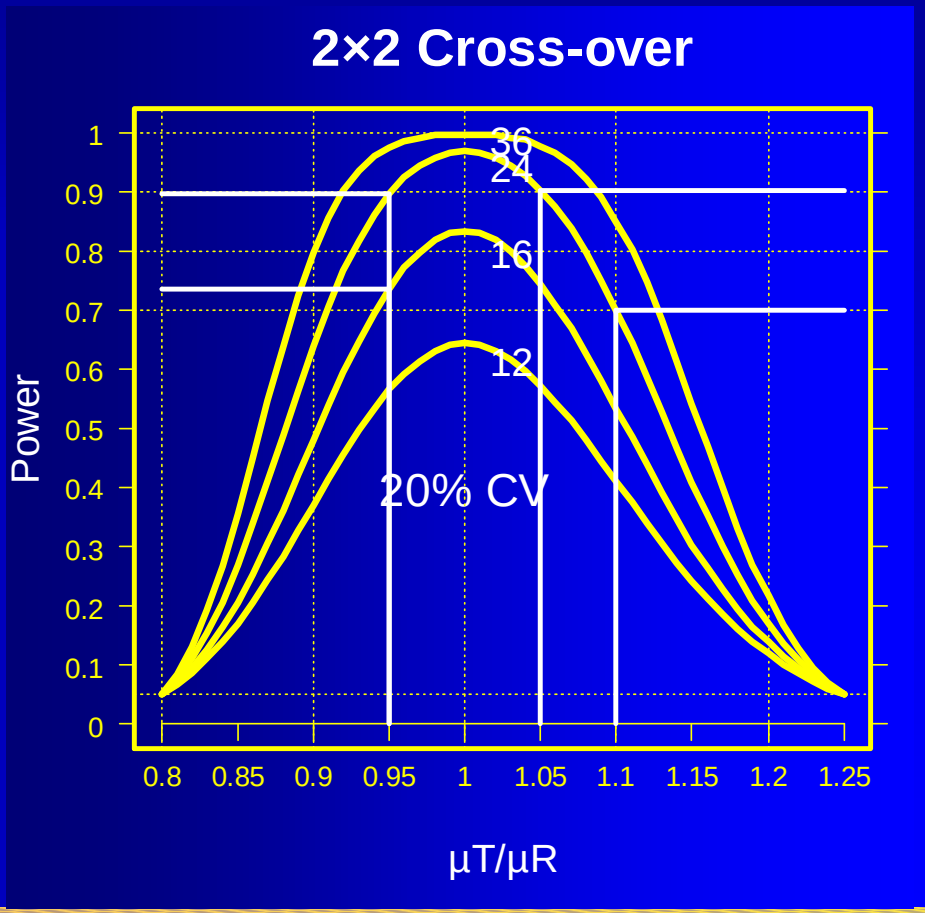
0.20 = 1/5

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

Power Curves

Power to show BE with 12 – 36 subjects for CV_{intra} 20%

n	24	↓	16:
power	0.896	→	0.735
μ_T/μ_R	1.05	↓	1.10:
power	0.903	→	0.700



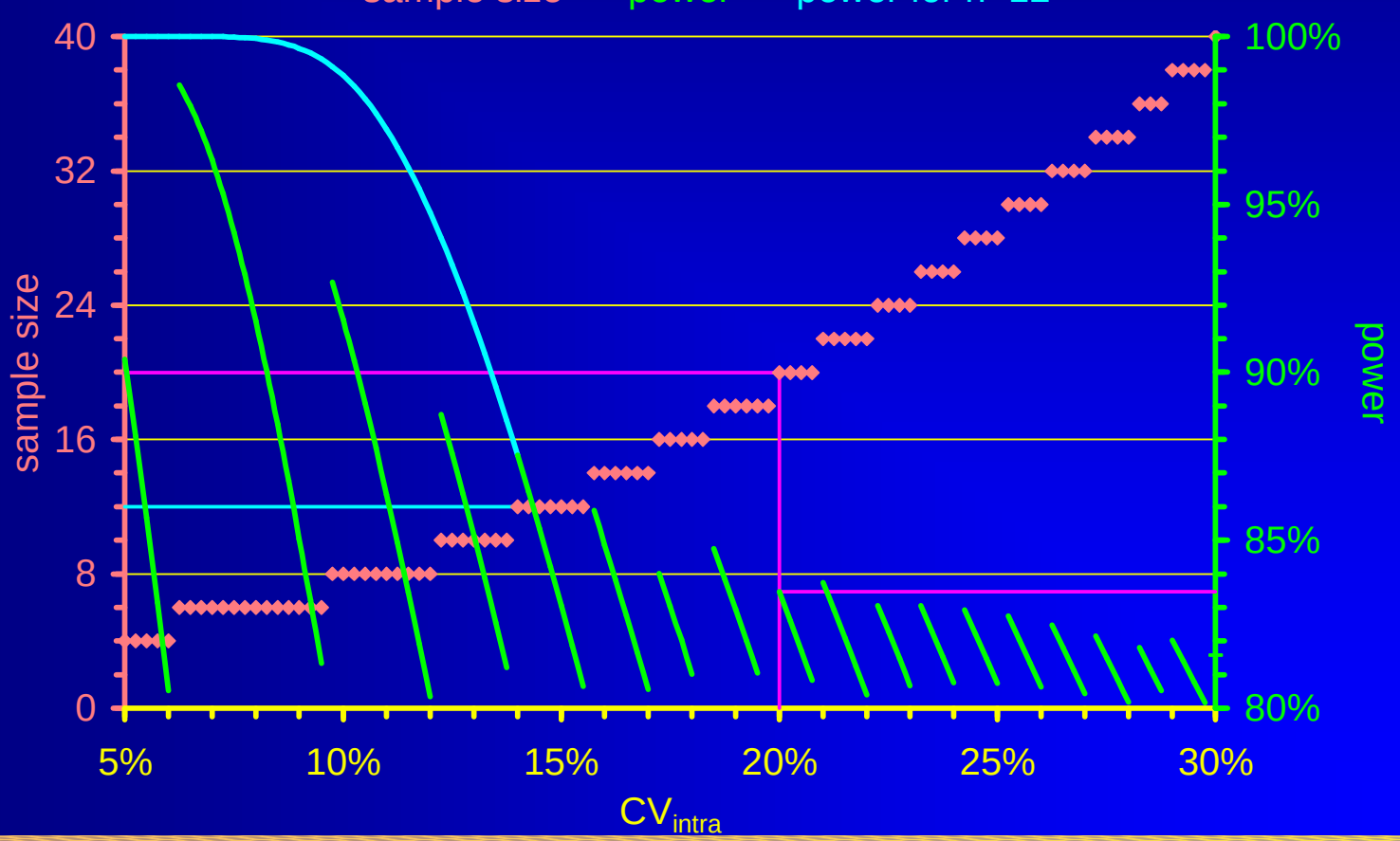
Power *vs.* Sample Size

- It is not possible to calculate the required sample size *directly*.
- Power is calculated instead; the smallest sample size which fulfills the minimum target power is used.
  - Example: α 0.05, target power 80% (β 0.2), T/R 0.95, CV_{intra} 20% → minimum sample size 19 (power 81%), rounded *up* to the next even number in a 2×2 study (power 83%).

n	power
16	73.54%
17	76.51%
18	79.12%
19	81.43%
20	83.47%

Power *vs.* Sample Size

2×2 cross-over, T/R 0.95, AR 80–125%, target power 80%



Background

- Reminder: Sample Size is not directly obtained – only power
- Solution given by DB Owen (1965) as a difference of two bivariate noncentral *t*-distributions
  - Definite integrals cannot be solved in closed form
    - 'Exact' methods rely on numerical methods (currently the most advanced is AS 243 of RV Lenth; implemented in R, FARTSSIE, EFG). nQuery uses an earlier version (AS 184).

Background

- Power estimations…
  - 'Brute force' methods (also called 'resampling' or 'Monte Carlo') converge asymptotically to the true power; need a good random number generator (*e.g.*, Mersenne Twister) and may be time-consuming
  - 'Asymptotic' methods use large sample approximations
- Approximations provide algorithms which should converge to the desired power based on the *t*-distribution

Sample Size (Guidelines)

- Recommended minimum
  - 12 WHO, EU, CAN, NZ, AUS, AR, MZ, ASEAN States, RSA, Russia (?)
  - 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

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 and/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.

Power & Sample Size

- **Reminder**
  - Generally power is set to at least 80% (β, error type II: producers's risk to get no approval for a bioequivalent formulation; power = 1 – β).
    1 out of 5 studies will fail just by chance!
  - If you plan for power of less than 70%, probably you will face problems with the ethics committee (ICH E9).
  - If you plan for power of more than 90% (especially with low variability drugs), problems with regulators are possible ('forced bioequivalence').
  - Add subjects ('alternates') according to the expected drop-out rate – especially for studies with more than two periods or multiple-dose studies.

US FDA, Canada TPD

- Statistical Approaches to Establishing Bioequivalence (2001)
  - Based on maximum difference of 5%.
  - Sample size based on 80 – 90% power.
- Draft GL (2010)*
  - Consider potency differences.
  - Sample size based on 80 – 90% power.
  - *Do not* interpolate linear between CVs (as stated in the GL)!

* All points removed in current (2012) GL.

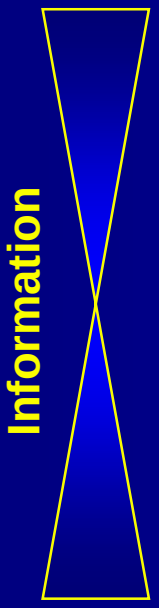
EU

- EMEA NfG on BA/BE (2001)
  - Detailed information (data sources, significance level, expected deviation of test from reference, desired power).
- EMA GL on BE (2010)
  - Batches must not differ more than 5% in actual content.
  - The number of subjects to be included in the study should be based on an appropriate sample size calculation.

Cookbook?

Hierarchy of Designs

- The more ‘sophisticated’ a design is, the more information can be extracted.
  - Hierarchy of designs:



Fully replicate (TRTR | RTRT, TRT | RTR)
Partial replicate (TRR | RTR | RRT)
Standard 2×2 cross-over (RT | RT)
Parallel (R | T)

  - Variances which can be estimated:

Parallel:	total variance (between + within)
2×2 Xover:	+ between, within subjects
Partial replicate:	+ within subjects (reference)
Full replicate:	+ within subjects (reference, test)

Coefficient(s) of Variation

- From any design one gets variances of *lower* design levels as well.
  - Total CV% from a 2×2 cross-over used in planning a parallel design study:
    - Intra-subject CV% (within)
    - Inter-subject CV% (between)
    - Total CV% (pooled)

$$CV_{\text{intra}}\,\% = 100 \cdot \sqrt{e^{MSE_W} - 1}$$

$$CV_{\text{inter}}\,\% = 100 \cdot \sqrt{e^{\frac{MSE_B - MSE_W}{2}} - 1}$$

$$CV_{\text{total}}\,\% = 100 \cdot \sqrt{e^{\frac{MSE_B + MSE_W}{2}} - 1}$$

Coefficient(s) of Variation

- However, CVs of *higher* design levels not available.
  - If only mean ± SD of reference is available…
    - Avoid 'rule of thumb' CV_{intra} = 60% of CV_{total}
    - Don't plan a cross-over based on CV_{total}
    - Examples (cross-over studies)

drug, formulation	design	n	metric	CV_{intra}	CV_{inter}	CV_{total}
methylphenidate MR	SD	12	AUC_t	7.00	19.1	20.4
paroxetine MR	MD	32	AUC_τ	25.2	55.1	62.1
lansoprazole DR	SD	47	C_{max}	47.0	25.1	54.6

    - Pilot study unavoidable, unless
    - Two-stage sequential design is used

Data from Pilot Studies

- Estimated CVs have a high degree of uncertainty (in the pivotal study it is more likely that you will be able to reproduce the PE, than the CV)
  - The smaller the size of the pilot, the more uncertain the outcome.
  - The more formulations you have tested, lesser degrees of freedom will result in worse estimates.
  - Remember: CV is an *estimate* – *not carved in stone!*

Pilot Studies: Sample Size

- Small pilot studies (sample size <12)
  - Are useful in checking the sampling schedule and
  - the appropriateness of the analytical method, but
  - are not suitable for the purpose of sample size planning!
  - Sample sizes (T/R 0.95, power ≥80%) based on a n = 10 pilot study

```
library(PowerTOST)
expsampleN.TOST(alpha=0.05,
  targetpower=0.80, theta1=0.80,
  theta2=1.25, theta0=0.95, CV=0.40,
  dfCV=24-2, alpha2=0.05, design="2x2")
```

CV%	CV		ratio
	fixed	uncertain	uncert./fixed
20	20	24	1.200
25	28	36	1.286
30	40	52	1.300
35	52	68	1.308
40	66	86	1.303

If pilot n=24: n=72, ratio 1.091

Pilot Studies: Sample Size

- Moderate sized pilot studies (sample size ~12–24) lead to more consistent results (both CV and PE).
  - If you stated a procedure in your protocol, even BE may be claimed in the pilot study, and no further study will be necessary (US-FDA).
  - If you have some previous hints of high intra-subject variability (>30%), a pilot study size of *at least* 24 subjects is reasonable. If you want reference-scaling, the pilot study has to be in a replicate design.
  - A Sequential Design avoids an unnecessarily large pilot study.

Pilot Studies: Sample Size

- *Do not* use the pilot study's CV, but calculate an upper confidence interval!
  - Gould (1995) recommends a 75% CI (*i.e.*, a producer's risk of 25%).
  - Apply Bayesian Methods (Julious and Owen 2006, Julious 2010) implemented in *R's PowerTOST/expsampleN.TOST*.
  - Unless you are under time pressure, a Two-Stage Sequential Design will help in dealing with the uncertain estimate from the pilot study.

Hints

- Literature search for CV%
  - Preferably other BE studies (the bigger, the better!)
  - PK interaction studies (Cave: Mainly in steady state! Generally lower CV than after SD).
  - Food studies (CV higher/lower than fasted!)
  - If CV_{intra} not given (quite often), a little algebra helps. All you need is the 90% geometric confidence interval and the sample size.

Algebra…

- Calculation of CV_{intra} from CI
  - Point estimate (PE) from the Confidence Limits

$$PE = \sqrt{CL_{lo} \cdot CL_{hi}}$$

  - Estimate the number of subjects / sequence (example 2×2 cross-over)
    - If total sample size (N) is an even number, *assume* (!)

$$n_1 = n_2 = ½N$$

    - If N is an odd number, *assume* (!)

$$n_1 = ½N + ½,\ n_2 = ½N - ½$$ (*not* $n_1 = n_2 = ½N$!)

  - Difference between one ***CL*** and the ***PE*** in log-scale; use the CL which is given with more significant digits

$$\Delta_{CL} = \ln PE - \ln CL_{lo} \quad or \quad \Delta_{CL} = \ln CL_{hi} - \ln PE$$

Algebra…

- Calculation of CV_{intra} from CI (cont'd)
  - Calculate the Mean Square Error (MSE)

$$MSE = 2\left(\frac{\Delta_{CL}}{\sqrt{\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}\cdot t_{1-2\cdot\alpha,n_1+n_2-2}}\right)^2$$

  - CV_{intra} from MSE as usual

$$CV_{\text{intra}}\,\% = 100\cdot\sqrt{e^{MSE}-1}$$

Algebra…

- Calculation of CV_{intra} from CI (cont'd)
  - Example: 90% CI [0.91 – 1.15], N 21 (n_1 = 11, n_2 = 10)

$$PE = \sqrt{0.91 \cdot 1.15} = 1.023$$

$$\Delta_{CL} = \ln 1.15 - \ln 1.023 = 0.11702$$

$$MSE = 2\left(\frac{0.11702}{\sqrt{\left(\frac{1}{11}+\frac{1}{10}\right)\times 1.729}}\right)^2 = 0.04798$$

$$CV_{\text{intra}}\,\% = 100 \times \sqrt{e^{0.04798} - 1} = 22.2\%$$

Algebra…

- **Proof: CI from calculated values**
  - **Example: 90% CI [0.91 – 1.15], N 21 (n_1 = 11, n_2 = 10)**

$$\ln PE = \ln\sqrt{CL_{lo}\cdot CL_{hi}} = \ln\sqrt{0.91\times 1.15} = 0.02274$$

$$SE_{\Delta} = \sqrt{\frac{2\cdot MSE}{N}} = \sqrt{\frac{2\times 0.04798}{21}} = 0.067598$$

$$CI = e^{\ln PE \pm t\cdot SE_{\Delta}} = e^{0.02274\pm 1.729\times 0.067598}$$

$$CI_{lo} = e^{0.02274-1.729\times 0.067598} = 0.91$$

$$CI_{hi} = e^{0.02274+1.729\times 0.067598} = 1.15$$

Sensitivity to Imbalance

- If the study was more imbalanced than assumed, the estimated CV is conservative
  - Example: 90% CI [0.89 – 1.15], N 24 (n_1 = 16, n_2 = 8, but not reported as such); CV 24.74% in the study

Balanced Sequences assumed…

n_1	n_2	CV%
12	12	26.29
13	11	26.20
14	10	25.91
15	9	25.43
16	8	24.74

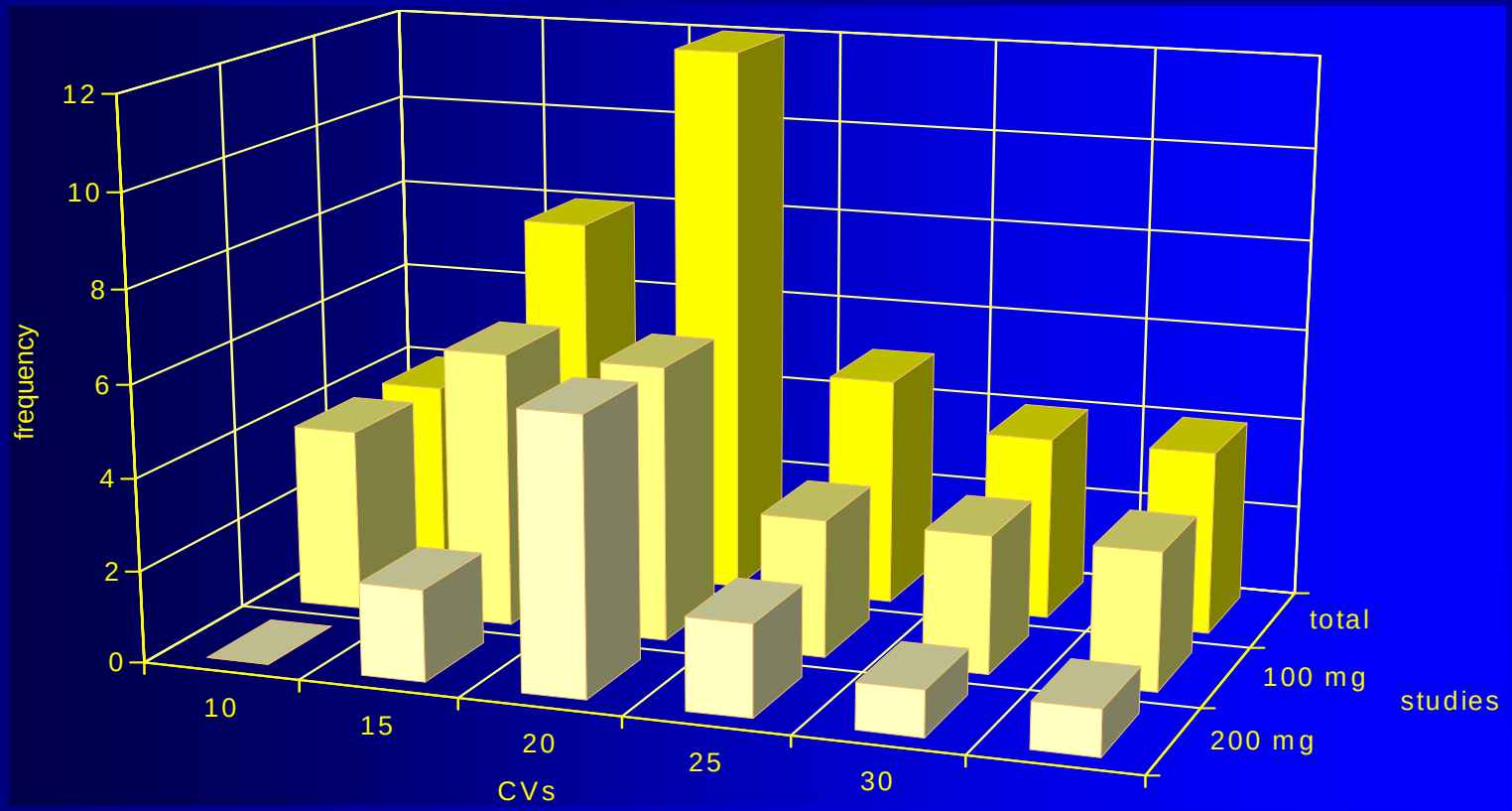
Sequences in study

No Algebra…

- **Implemented in *R*-package *PowerTOST*, function *CVfromCI* (not only 2×2 cross-over, but also parallel groups, higher order cross-overs, replicate designs). Example:**

```
library(PowerTOST)
CVfromCI(lower=0.91, upper=1.15, n=21, design="2x2", alpha=0.05)
[1] 0.2219886
```

Literature data



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

Pooling of CV%

- Intra-subject CV from different studies can be pooled (LA Gould 1995, Patterson and Jones 2006)
  - In the parametric model of log-transformed data, additivity of variances (not of CVs!) apply.
  - Do not use the arithmetic mean (or the geometric mean either) of CVs.
  - Before pooling variances must be weighted acccording to the studies' sample size and sequences
    - Larger studies are more influentual than smaller ones.
    - More sequences (with the same n) give higher CV.

Pooling of CV%

- Intra-subject CV from different Xover studies
  - Calculate the variance from CV

$$\sigma_w^2 = \ln(CV_{\text{intra}}^2 + 1)$$

  - Calculate the total variance weighted by df

$$\sum \sigma_w^2 df$$

  - Calculate the pooled CV from total variance

$$CV = \sqrt{e^{\sum \sigma_w^2 df / \sum df} - 1}$$

  - Optionally calculate an upper (1–α) % confidence limit on the pooled CV (recommended α = 0.25)

$$CL_{CV} = \sqrt{e^{\sum \sigma_w^2 df / \chi^2_{\alpha, \sum df}} - 1}$$

Pooling of CV%

- Degrees of freedom of various Xover designs

Name	df	Name in PowerTOST
2×2×2 cross over	n – 2	2x2
3×3 Latin Squares	2n – 4	3x3
6 sequence Williams' design	2n – 4	3x6x3
4×4 Latin Squares, Williams' design	3n – 6	4x4
2×2×3 fully replicated design	2n – 3	2x2x3
2×2×4 fully replicated design	3n – 4	2x2x4
2×4×4 fully replicated design	3n – 4	2x4x4
2×3×3 partial replicate design	2n – 3	2x3x3

Pooling of CV%

- **Example: 3 studies, different Xover designs**

CV_{intra}	n	seq.	df	σ_W	σ^2_W	$\sigma^2_W \times df$
15%	**12**	**6**	20	0.149	0.0223	0.4450
25%	**16**	**2**	14	0.246	0.0606	0.8487
20%	**24**	**2**	22	0.198	0.0392	0.8629
N	52	Σ	56		Σ	2.1566

$\sqrt{2.1566/56}$

σ_{pooled}	σ^2_{pooled}
0.196	0.0385

$2\times n-4$

$n-2$

$100\sqrt{e^{0.0385}-1}$

CV_{pooled}	$CV_{g.mean}$
19.81%	~~**19.57%**~~

α	$1-\alpha$	$\chi^2_{(\alpha,df)}$		
0.25	0.75	48.546	21.31%	+7.6%

$100\sqrt{e^{56\times 0.0385/48.546}-1}$

Pooling of CV%

- *R* **package** *PowerTost* **function** *CVpooled*, **example's data.**

```
library(PowerTOST)
CVs <- "
  PKmetric |  CV   |  n | design | source
     AUC   | 0.15 | 12 | 3x6x3  | study 1
     AUC   | 0.25 | 16 | 2x2    | study 2
     AUC   | 0.20 | 24 | 2x2    | study 3
")
txtcon <- textConnection(CVs)
CVdata <- read.table(txtcon, header=TRUE, sep="|",
            strip.white=TRUE, as.is=TRUE)
close(txtcon)
CVsAUC <- subset(CVdata,PKmetric=="AUC")
print(CVpooled(CVsAUC, alpha=0.25), digits=4, verbose=TRUE)

Pooled CV = 0.1981 with 56 degrees of freedom
Upper 75% confidence limit of CV = 0.2131
```

Pooling of CV%

- Or you may combine pooling with an estimated sample size based on uncertain CVs (we will see later what that means).
  R package *PowerTost* function *expsampleN.TOST*, data of last example.
  CVs and degrees of freedom must be given as vectors:
  CV = c(0.15,0.25,0.2), dfCV = c(20,14,22)

Pooling of CV%

```
library(PowerTOST)
expsampleN.TOST(alpha=0.05,
  targetpower=0.8, theta0=0.95,
  CV=c(0.15,0.25,0.2),
  dfCV=c(20,14,22),
  alpha2=0.25, design="2x2",
  print=TRUE, details=TRUE)
```

```
++++++++ Equivalence test - TOST ++++++++
   Sample size est. with uncertain CV
------------------------------------------
Study design:  2x2 crossover
Design characteristics:
df = n-2, design const. = 2, step = 2
log-transformed data (multiplicative model)
alpha = 0.05, target power = 0.8
BE margins        = 0.8 ... 1.25
Null (true) ratio = 0.95
Variability data
   CV df
 0.15 20
 0.25 14
 0.20 22
CV(pooled)          = 0.1981467 with 56 df
one-sided upper CL = 0.2131329 (level = 75%)

Sample size search
 n    exp. power
16   0.733033
18   0.788859
20   0.832028
```

Pooling of CV%

- ‘Doing the maths’ is just the first part of the job!
  - Does it make sense to pool studies of different ‘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 CV (matrix effects!).
    - Generally we have insufficient information about the clinical setup (*e.g.* posture control).
    - Review studies critically; don’t try to mix oil with water.

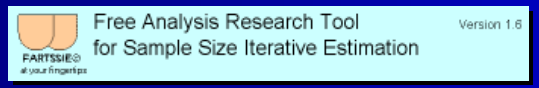
Tools

- 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!

Approximations obsolete

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



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/

```
library(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')
```

Comparison

original values	Method	Algorithm	CV% 5	7.5	10	12	12.5	14	15	16	17.5	18	20	22
PowerTOST 1.1-02 (2013)	exact	Owen's Q	4	6	8	8	10	12	12	14	16	16	20	22
Patterson & Jones (2006)	noncentr. *t*	AS 243	4	5	7	8	9	11	12	13	15	16	19	22
Diletti *et al.* (1991)	noncentr. *t*	Owen's Q	4	5	7	NA	9	NA	12	NA	15	NA	19	NA
nQuery Advisor 7 (2007)	noncentr. *t*	AS 184	4	6	8	8	10	12	12	14	16	16	20	22
FARTSSIE 1.7 (2010)	noncentr. *t*	AS 243	4	5	7	8	9	11	12	13	15	16	19	22
EFG 2.01 (2009)	noncentr. *t*	AS 243	4	5	7	8	9	11	12	13	15	16	19	22
	brute force	ElMaestro	4	5	7	8	9	11	12	13	15	16	19	22
StudySize 2.0.1 (2006)	central *t*	?	NA	5	7	8	9	11	12	13	15	16	19	22
Hauschke *et al.* (1992)	approx. *t*		NA	NA	8	8	10	12	12	14	16	16	20	22
Chow & Wang (2001)	approx. *t*		NA	6	6	8	8	10	12	12	14	16	18	22
Kieser & Hauschke (1999)	approx. *t*		2	NA	6	8	NA	10	12	14	NA	16	20	24

original values	Method	Algorithm	CV% 22.5	24	25	26	27.5	28	30	32	34	36	38	40
PowerTOST 1.1-02 (2013)	exact	Owen's Q	24	26	28	30	34	34	40	44	50	54	60	66
Patterson & Jones (2006)	noncentr. *t*	AS 243	23	26	28	30	33	34	39	44	49	54	60	66
Diletti *et al.* (1991)	noncentr. *t*	Owen's Q	23	NA	28	NA	33	NA	39	NA	NA	NA	NA	NA
nQuery Advisor 7 (2007)	noncentr. *t*	AS 184	24	26	28	30	34	34	40	44	50	54	60	66
FARTSSIE 1.7 (2010)	noncentr. *t*	AS 243	23	26	28	30	33	34	39	44	49	54	60	66
EFG 2.01 (2009)	noncentr. *t*	AS 243	23	26	28	30	33	34	39	44	49	54	60	66
	brute force	ElMaestro	23	26	28	30	33	34	39	44	49	54	60	66
StudySize 2.0.1 (2006)	central *t*	?	23	26	28	30	33	34	39	44	49	54	60	66
Hauschke *et al.* (1992)	approx. *t*		24	26	28	30	34	36	40	46	50	56	64	70
Chow & Wang (2001)	approx. *t*		24	26	28	30	34	34	38	44	50	56	62	68
Kieser & Hauschke (1999)	approx. *t*		NA	28	30	32	NA	38	42	48	54	60	66	74

Sample size tables

- **Diletti E, Hauschke D, and VW Steinijans**

Sample size determination for bioequivalence assessment by means of confidence intervals
Int J Clin Pharmacol Ther Toxicol 29(1), 1–8 (1991)

α 0.05, Δ 0.2 [0.80 – 1.25], Power 80%								
CV%	PE (GMR, T/R)							
	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	11	5	4	4	4	5	7	22
7.5	21	7	5	5	5	7	12	44
10.0	35	11	7	6	7	10	20	75
12.5	54	16	9	8	9	14	30	117
15.0	77	22	12	10	12	19	41	167
17.5	103	29	15	13	15	25	56	226
20.0	134	37	19	16	18	32	72	293
22.5	168	46	23	19	23	39	90	368
25.0	206	56	28	23	27	48	110	452
27.5	247	67	33	27	33	57	132	543
30.0	292	79	39	32	38	67	155	641

α 0.05, Δ 0.2 [0.80 – 1.25], Power 90%								
CV%	PE (GMR, T/R)							
	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	14	6	4	4	4	5	8	28
7.5	28	9	6	5	6	8	16	60
10.0	48	14	8	7	8	13	26	104
12.5	74	21	11	9	11	18	40	161
15.0	106	29	15	12	15	25	57	231
17.5	142	39	20	15	19	34	75	312
20.0	185	50	26	19	24	43	99	405
22.5	232	63	31	23	30	54	124	509
25.0	284	77	37	28	36	65	151	625
27.5	342	92	44	34	43	78	181	751
30.0	403	108	52	39	51	92	214	888

Sample size tables

- **Tóthfalusi L and L Endrényi**

  Sample Sizes for Designing Bioequivalene Studies for Highly Variable Drugs

  J Pharm Pharmaceut Sci 15(1), 73–84 (2011)

α 0.05, ABEL (EMA), partial repl., Power 80%								
CV%	PE (GMR, T/R)							
	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
30	194	53	27	22	26	45	104	>201
35	127	51	29	25	29	45	84	>201
40	90	44	29	27	30	42	68	139
45	77	40	29	27	29	37	57	124
50	75	40	30	28	30	37	53	133
55	81	42	32	30	32	40	56	172
60	88	46	36	33	36	44	63	>201
65	99	53	40	37	40	50	71	>201
70	109	58	45	41	45	56	80	>201
75	136	67	50	46	50	62	89	>201
80	144	72	54	51	55	68	97	>201

α 0.05, RSABE (FDA), partial repl., Power 80%								
CV%	PE (GMR, T/R)							
	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
30	145	45	24	21	24	39	82	>201
35	74	37	24	22	25	34	54	109
40	60	33	24	22	24	31	47	104
45	59	31	23	22	24	29	43	116
50	66	30	24	22	23	28	41	133
55	80	30	24	22	24	28	44	172
60	88	31	24	23	24	30	50	>201
65	98	32	25	24	25	31	53	>201
70	106	35	26	25	26	31	62	>201
75	136	38	27	26	27	34	70	>201
80	144	40	40	27	29	37	76	>201

Sample size tables

- Never interpolate!
- Use the most conservative cell entry
  (higher CV, PE away from 1)

Example: Sample size for CV 18%, PE 0.92, 80% power?

CV%	PE (GMR, T/R)		
	0.90	0.95	1.00
17.5	29	15	13
20.0	37	19	16

CV%	PE (GMR, T/R)		
	0.90	0.95	1.00
17.5	29	15	13
20.0	37	19	16

Round up to next even number (38)

Tables *vs.* calculations

- The penalty to be paid using tables might be high – especially if uprounding has to be applied.

  Sample sizes of the example: CV 18%, PE 0.92, 80% power

  - Table: n = 38
  - Approximations
    - Hauschke *et al.* 1992: n = 24
    - Chow and Wang 2001: n = 22
    - FARTSSIE.xls: n = 22
  - Exact: n = 22

Tables *vs.* calculations

- If we planned the study in 38 subjects (tables) instead of the required 22 (exact) we gain a lot of power, but how much?
  - n = 22: power 80.55%
  - n = 38: power 95.56%
- If step sizes are too wide, calculations mandatory
- *PowerTOST* supports simulations for ABEL (EMA-method) and RSABE (FDA-method)

Tables *vs.* calculations

```
library(PowerTOST)
sampleN.scABEL(CV=0.40, details=F)

++++++ scaled (widened) ABEL +++++++
       Sample size estimation
-----------------------------------
Study design:  2x3x3
log-transformed data (multiplicative
model)
1e+05 studies simulated.

alpha  = 0.05, target power = 0.8
CVw(T) = 0.4; CVw(R) = 0.4
Null (true) ratio = 0.95
ABE limits/PE constraints = 0.8…1.25
Regulatory settings: EMA
- CVswitch =  0.3, cap on ABEL
  if CV > 0.5
- Regulatory constant = 0.76

Sample size
 n     power
30   0.827170
```

```
library(PowerTOST)
sampleN.RSABE(CV=0.40, details=F)

++++ Reference scaled ABE crit. ++++
     Sample size estimation
-------------------------------------
Study design:  2x3x3
log-transformed data (multiplicative
model)
1e+05 studies simulated.

alpha  = 0.05, target power = 0.8
CVw(T) = 0.4; CVw(R) = 0.4
Null (true) ratio = 0.95
ABE limits/PE constraints = 0.8…1.25
Regulatory settings: FDA

Sample size
 n     power
24   0.808640
```

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.

Sensitivity Analysis

- **Example**

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

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%

Sensitivity Analysis

- **Example**

  PowerTOST*, function *sampleN.TOST

```
library(PowerTOST)
sampleN.TOST(alpha=0.05, targetpower=0.9, theta0=0.95,
             CV=0.2, design="2x2", print=TRUE)

++++++++++++ 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
```

Sensitivity Analysis

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

```
library(PowerTOST)
power.TOST(alpha=0.05, theta0=0.95, CV=0.25, n=26, design="2x2")
[1] 0.7760553

power.TOST(alpha=0.05, theta0=0.95, CV=0.20, n=22, design="2x2")
[1] 0.8688866

power.TOST(alpha=0.05, theta0=0.95, CV=0.25, n=22, design="2x2")
[1] 0.6953401

power.TOST(alpha=0.05, theta0=0.90, CV=0.20, n=26, design="2x2")
[1] 0.6694514

power.TOST(alpha=0.05, theta0=0.90, CV=0.25, n=22, design="2x2")
[1] 0.4509864
```

Sensitivity Analysis

- Must be done *before* the study *(a priori)*
- The Myth of retrospective (*a posteriori*) Power…
  - High values do not further support the claim of already demonstrated bioequivalence.
  - Low values do not invalidate a bioequivalent formulation.
  - Further reader:

RV Lenth (2000)
JM Hoenig and DM Heisey (2001)
P Bacchetti (2010)

Thank You!

Sample Size Estimation for BE Studies

Open Questions?

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

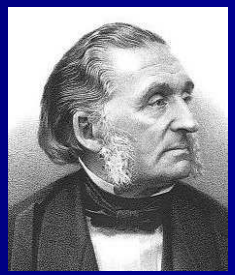
To bear in Remembrance...

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

The Myth of Power

There is simple intuition behind results like these: If my car made it to the top of the hill, then it is powerful enough to climb that hill; if it didn't, then it obviously isn't powerful enough. Retrospective power is an obvious answer to a rather uninteresting question. A more meaningful question is to ask whether the car is powerful enough to climb a particular hill never climbed before; or whether a different car can climb that new hill. Such questions are prospective, not retrospective.

The fact that retrospective power adds no new information is harmless in its own right. However, in typical practice, it is used to exaggerate the validity of a significant result ("not only is it significant, but the test is really powerful!"), or to make excuses for a nonsignificant one ("well, P is .38, but that's only because the test isn't very powerful"). The latter case is like blaming the messenger.

RV Lenth
Two Sample-Size Practices that I don't recommend
http://www.math.uiowa.edu/~rlenth/Power/2badHabits.pdf

References

- Collection of links to global documents
  http://bebac.at/Guidelines.htm
- ICH
  - E9: Statistical Principles for Clinical Trials (1998)
- EMA-CPMP/CHMP/EWP
  - Points to Consider on Multiplicity Issues in Clinical Trials (2002)
  - BA/BE for HVDs/HVDPs: Concept Paper (2006)
    http://bebac.at/downloads/14723106en.pdf
  - Questions & Answers on the BA and BE Guideline (2006)
    http://bebac.at/downloads/4032606en.pdf
  - Draft Guideline on the Investigation of BE (2008)
  - Guideline on the Investigation of BE (2010)
  - Questions & Answers: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics (2013)
- US-FDA
  - Center for Drug Evaluation and Research (CDER)
    - Statistical Approaches Establishing Bioequivalence (2001)
    - Bioequivalence Recommendations for Specific Products (2007)

- Midha KK, Ormsby ED, Hubbard JW, McKay G, Hawes EM, Gavalas L, and IJ McGilveray
  Logarithmic Transformation in Bioequivalence: Application with Two Formulations of Perphenazine
  J Pharm Sci 82(2), 138–44 (1993)
- Hauschke D, Steinijans VW, and E Diletti
  Presentation of the intrasubject coefficient of variation for sample size planning in bioequivalence studies
  Int J Clin Pharmacol Ther 32(7), 376–78 (1994)
- Diletti E, Hauschke D, and VW Steinijans
  Sample size determination for bioequivalence assessment by means of confidence intervals
  Int J Clin Pharm Ther Toxicol 29(1), 1–8 (1991)
- Hauschke D, Steinijans VW, Diletti E, and M Burke
  Sample Size Determination for Bioequivalence Assessment Using a Multiplicative Model
  J Pharmacokin Biopharm 20(5), 557–61 (1992)
- S-C Chow and H Wang
  On Sample Size Calculation in Bioequivalence Trials
  J Pharmacokin Pharmacodyn 28(2), 155–69 (2001)
  Errata: J Pharmacokin Pharmacodyn 29(2), 101–2 (2002)
- DB Owen
  A special case of a bivariate non-central t-distribution
  Biometrika 52(3/4), 437–46 (1965)

References

- LA Gould
  Group Sequential Extension of a Standard Bioequivalence Testing Procedure
  J Pharmacokin Biopharm 23(1), 57–86 (1995)
  DOI: 10.1007/BF02353786
- Jones B and MG Kenward
  Design and Analysis of Cross-Over Trials
  Chapman & Hall/CRC, Boca Raton (2nd Edition 2000)
- Hoenig JM and DM Heisey
  The Abuse of Power: The Pervasive Fallacy of Power Calculations for Data Analysis
  The American Statistician 55(1), 19–24 (2001)
  http://www.vims.edu/people/hoenig_jm/pubs/hoenig2.pdf
- SA Julious
  Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data
  Statistics in Medicine 23(12), 1921–86 (2004)
- Julious SA and RJ Owen
  Sample size calculations for clinical studies allowing for uncertainty about the variance
  Pharmaceutical Statistics 5/1, 29-37 (2006)
- Patterson S and B Jones
  Determining Sample Size, in:
  Bioequivalence and Statistics in Clinical Pharmacology
  Chapman & Hall/CRC, Boca Raton (2006)
- Tóthfalusi L, Endrényi L, and A Garcia Arieta
  Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence
  Clin Pharmacokinet 48(11), 725–43 (2009)
- SA Julious
  Sample Sizes for Clinical Trials
  Chapman & Hall/CRC, Boca Raton (2010)
- P Bacchetti
  Current sample size conventions: Flaws, harms, and alternatives
  BMC Medicine 8(17), (2010)
  http://www.biomedcentral.com/content/pdf/1741-7015-8-17.pdf
- Tóthfalusi L and L Endrényi
  Sample Sizes for Designing Bioequivalene Studies for Highly Variable Drugs
  J Pharm Pharmaceut Sci 15(1), 73–84 (2011)
  http://ejournals.library.ualberta.ca/index.php/JPPS/article/download/11612/9489
- D Labes
  Package 'PowerTOST'
  Version 1.1-10 (2014-01-31)
  http://cran.r-project.org/web/packages/PowerTOST/PowerTOST.pdf