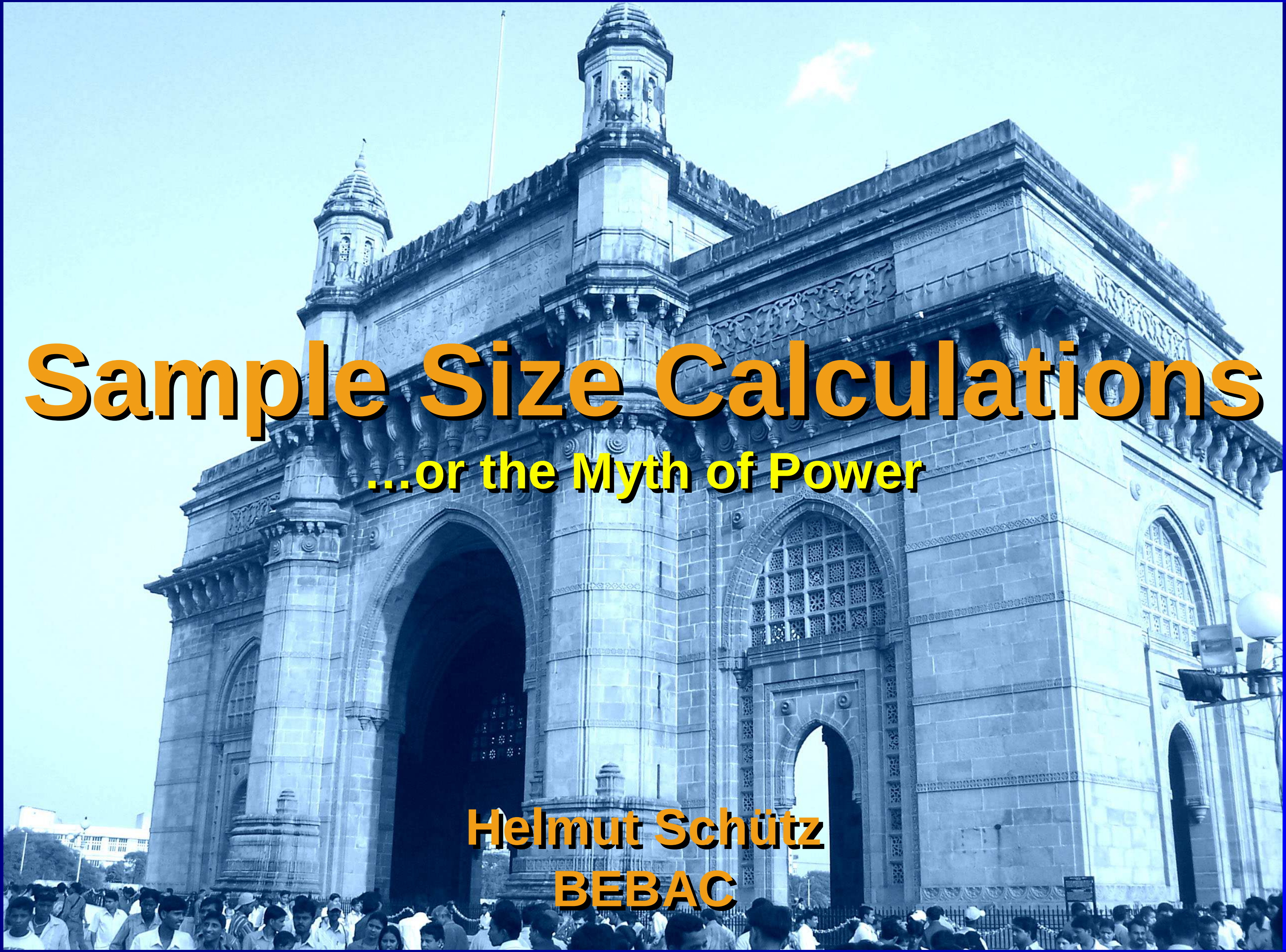

Sample Size Calculations

…or the Myth of Power

Helmut Schütz
BEBAC

BE BAC

Sample Size (Limits)

- Minimum
  - 12: WHO, EU, CAN, NZ, AUS, AR, MZ, ASEAN States, RSA
  - 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.'
  - 20: RSA (MR formulations)
  - 24: Saudia Arabia (12 to 24 if statistically justifiable)
  - 24: Brazil
  - Sufficient number: JPN

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.'

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%, problems with the ethics committee are likely (ICH E9).
  - If you plan for power of more than 90% (especially with low variability drugs), problems with the regulator 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)!

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EU

- EMEA NfG on BA/BE (2001)
  - Detailed information (data sources, significance level, expected deviation, desired power).
- EMA GL on BE (2010)
  - Batches must not differ more than 5%.
  - 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:

    Full replicate (TRTR | RTRT)

    Partial replicate (TRR | RTR | RRT)

    Standard 2×2 cross-over (RT | RT)

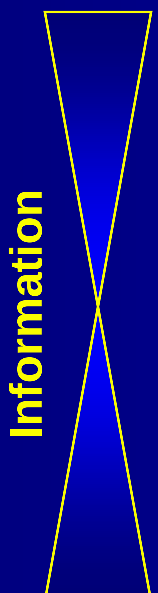
    Parallel (R | T)
  - Variances which can be estimated:

    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 also.
  - Total CV% from a 2×2 cross-over used in planning a parallel design study:
    - Intra-subject CV% (within) → $CV_{\text{intra}}\% = 100 \cdot \sqrt{e^{MSE_W} - 1}$
    - Inter-subject CV% (between) → $CV_{\text{inter}}\% = 100 \cdot \sqrt{e^{\frac{MSE_B - MSE_W}{2}} - 1}$
    - Total CV% (pooled) → $CV_{\text{total}}\% = 100 \cdot \sqrt{e^{\frac{MSE_B + MSE_W}{2}} - 1}$

Coefficient(s) of Variation

- 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}	$\%_{intra/total}$
methylphenidate MR	SD	12	AUC_t	7.00	19.1	20.4	34.3
paroxetine MR	MD	32	AUC_τ	25.2	55.1	62.1	40.6
lansoprazole DR	SD	47	C_{max}	47.0	25.1	54.6	86.0

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

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

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

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…

Sequences in study

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

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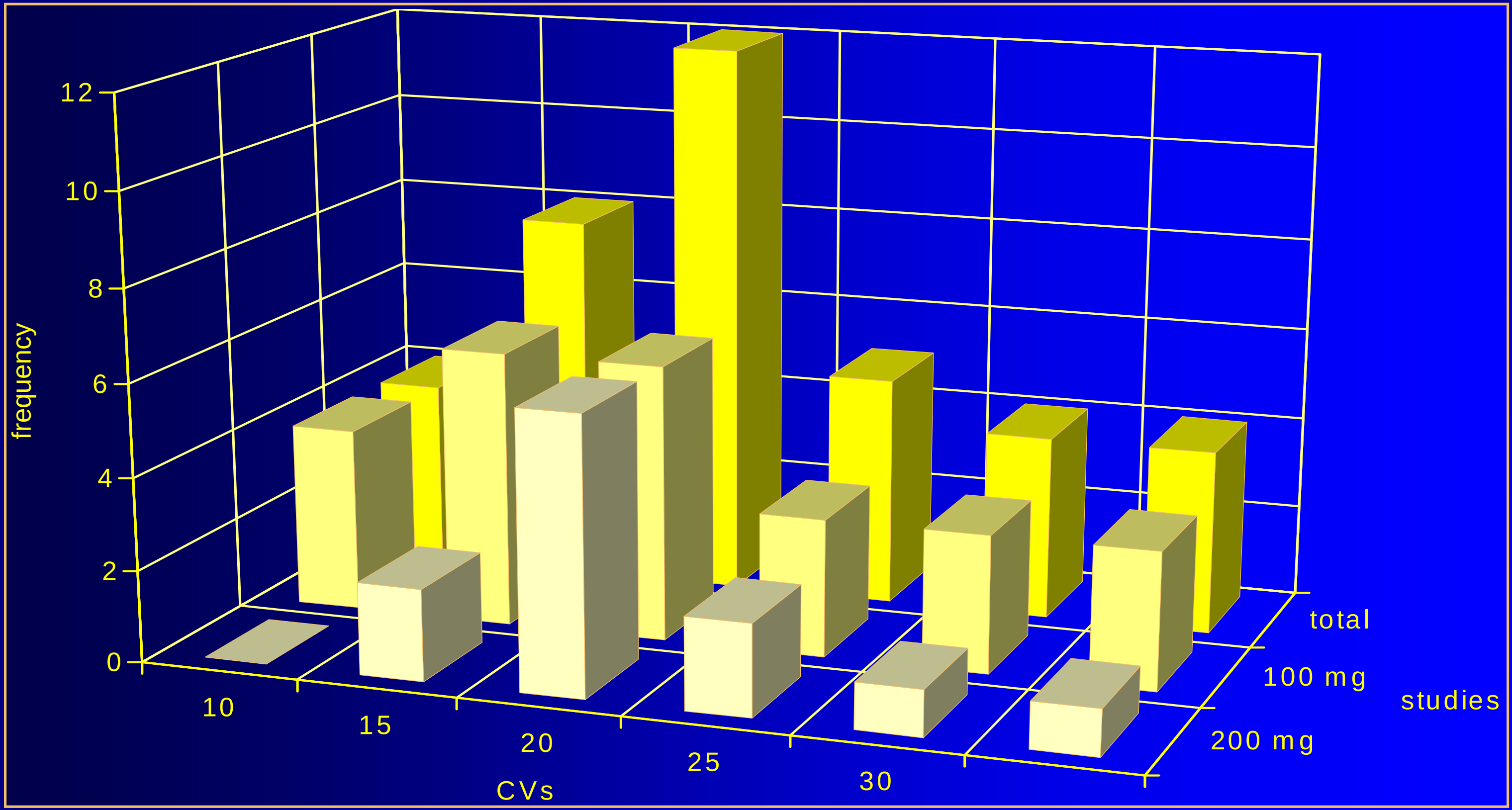
No Algebra…

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

```
require(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 – larger studies are more influentual than smaller ones.

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Pooling of CV%

- Intra-subject CV from different 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%

- Example 1: $n_1=n_2$;
  $CV_{Study1} < CV_{Study2}$

studies	N
2	24

df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
20	0.25	0.75	1.2540	**0.254**	~~0.245~~
		$\chi^2_{(\alpha,df)}$	15.452	0.291	+14.3%

CV_{intra}	n	seq.	df (mj)	σ_W	σ^2_W	$\sigma^2_W \times$ df	CV_{intra} / pooled	>CL_{upper}
0.200	**12**	**2**	10	0.198	0.0392	0.3922	78.6%	no
0.300	**12**	**2**	10	0.294	0.0862	0.8618	117.9%	yes

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Pooling of CV%

- Example 2: $n_1<n_2$; $CV_{Study1} < CV_{Study2}$

studies	N
2	36

df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
32	0.25	0.75	2.2881	**0.272**	~~0.245~~
		$\chi^2_{(\alpha,df)}$	26.304	0.301	+10.7%

CV_{intra}	n	seq.	df (mj)	σ_W	σ^2_W	$\sigma^2_W \times df$	$CV_{intra / pooled}$	$>CL_{upper}$
0.200	**12**	**2**	10	0.198	0.0392	0.3922	73.5%	no
0.300	**24**	**2**	22	0.294	0.0862	1.8959	110.2%	no

Pooling of CV%

- Example 3: $n_1 > n_2$; $CV_{Study1} < CV_{Study2}$

studies	N
2	36

df (total)	α	$1-\alpha$	total	CV_{pooled}	CV_{mean}
32	0.25	0.75	1.7246	**0.235**	~~0.245~~
		$\chi^2_{(\alpha,df)}$	26.304	0.260	+10.6%

CV_{intra}	n	seq.	df (mj)	σ_W	σ^2_W	$\sigma^2_W \times$ df	CV_{intra} / pooled	>CL_{upper}
0.200	**24**	**2**	22	0.198	0.0392	0.8629	85.0%	no
0.300	**12**	**2**	10	0.294	0.0862	0.8618	127.5%	yes

Pooling of CV%

- *R* package *PowerTost* function *CVpooled*, data of last example.

```
require(PowerTOST)
CVs <- ("
  PKmetric |  CV  |  n | design | source
     AUC   | 0.20 | 24 |  2x2   | study 1
     AUC   | 0.30 | 12 |  2x2   | study 2
")
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=3, verbose=TRUE)

Pooled CV = 0.235 with 32 degrees of freedom
Upper 75% confidence limit of CV = 0.260
```

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(0.2,0.3), dfCV = c(22,10)

Pooling of CV%

```
require(PowerTOST)
expsampleN.TOST(alpha=0.05,
  targetpower=0.8,
  theta1=0.8, theta2=1.25,
  theta0=0.95, CV=c(0.2,0.3),
  dfCV=c(22,10), alpha2=0.05,
  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
 0.2 22
 0.3 10
CV(pooled)         = 0.2353158 with 32 df
one-sided upper CL = 0.2995364 (level = 95%)

Sample size search
 n    exp. power
24   0.766585
26   0.800334
```

α- vs. β-Error

- α-Error: Patient's risk to be treated with a bioinequivalent formulation.
  - Although α is generally set to 0.05, sometimes <0.05 (*e.g.*, NTDIs in Brazil, multiplicity, interim analyses).
- β-Error: Producer's risk to get no approval for a bioequivalent formulation.
  - Generally *set* in study planning to ≤0.2, where power = 1 – β = ≥80%.
  - There is no *a posteriori* (aka *post hoc*) power! **Either a study has demonstrated BE or not.** Phoenix'/WinNonlin's output is statistical nonsense!

Power Curves

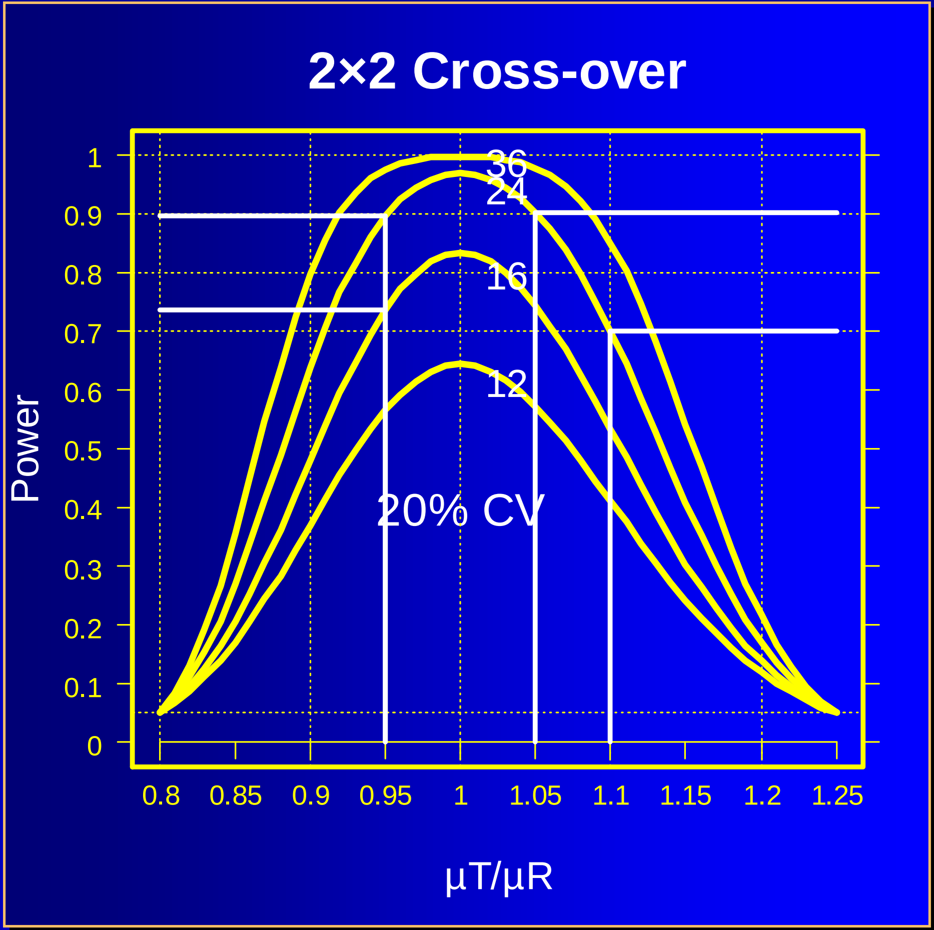
Power to show

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

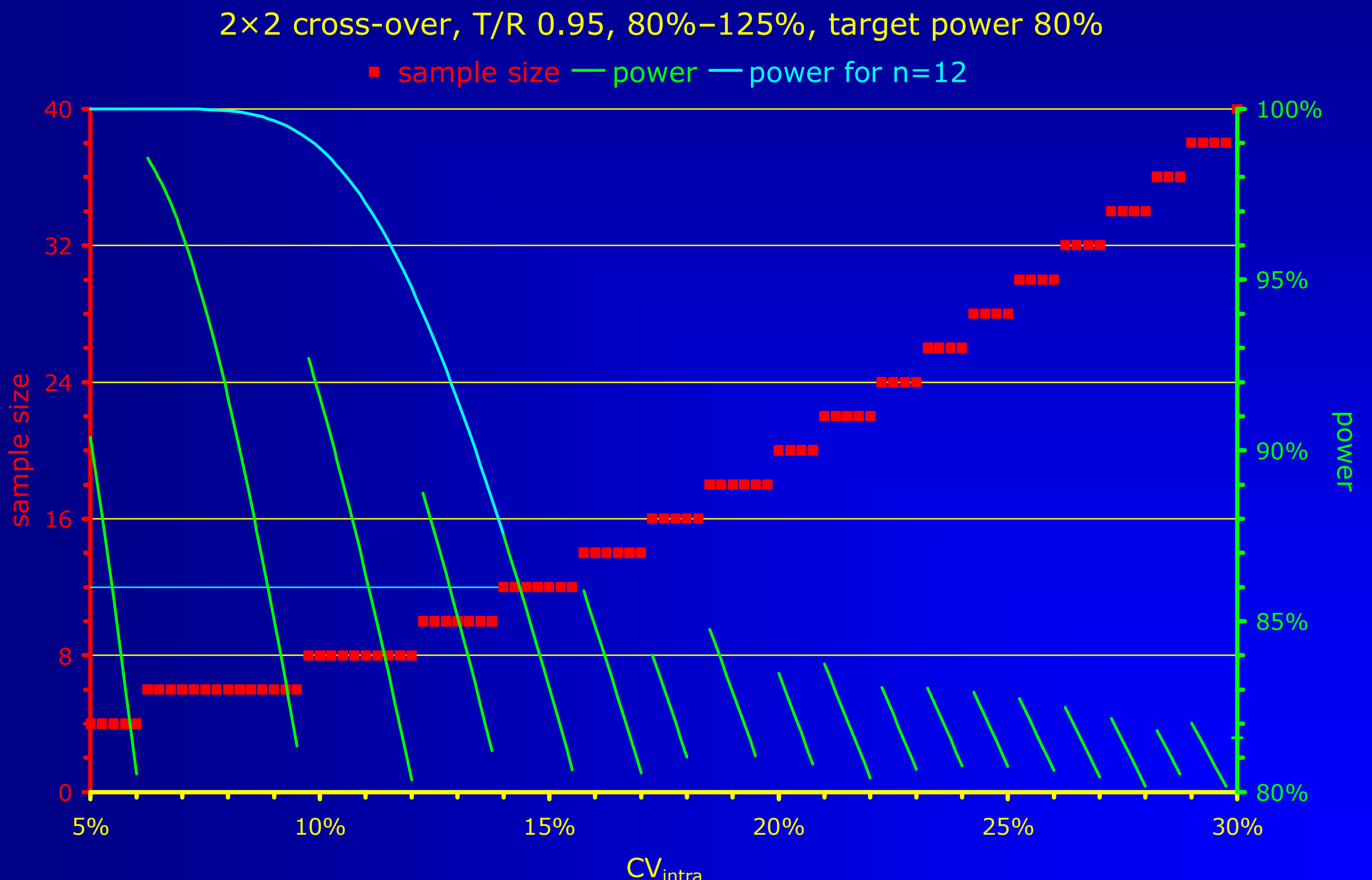


Power *vs.* Sample Size

- It is not possible to *directly* calculate the required sample size.
- Power is calculated instead, and the lowest 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% $\rightarrow$ 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



Tools

- Sample Size Tables (Phillips, Diletti, Hauschke, Chow, Julious, …)
- Approximations (Diletti, Chow, Julious, …)
- General purpose (SAS, *R*, S+, StaTable, …)
- Specialized Software (nQuery Advisor, PASS, FARTSSIE, StudySize, …)
- Exact method (Owen – implemented in *R*-package *PowerTOST*)*

* Thanks to Detlew Labes!

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 calculations…
  - '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

Comparison

original values	Method	Algorithm	CV% 5	7.5	10	12	12.5	14	15	16	17.5	18	20	22
PowerTOST 0.8-2 (2011)	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 1.6 (2008)	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 0.8-2 (2011)	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 1.6 (2008)	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

Approximations

Hauschke *et al.* (1992)

Patient's risk α 0.05, Power 80% (Producer's risk β 0.2), AR [0.80 – 1.25], CV 0.2 (20%), T/R 0.95

1. $\Delta = \ln(0.8) - \ln(T/R) = -0.1719$
2. Start with e.g. n=8/sequence
   1. $df = n \cdot 2 - 1 = 8 \times 2 - 1 = 14$
   2. $t_{\alpha,df} = 1.7613$
   3. $t_{\beta,df} = 0.8681$
   4. new $n = [(t_{\alpha,df} + t_{\beta,df})^2 \cdot (CV/\Delta)]^2 =$ $(1.7613+0.8681)^2 \times (-0.2/0.1719)^2 = 9.3580$
3. Continue with n=9.3580/sequence (N=18.716 → 19)
   1. df = 16.716; roundup to the next integer 17
   2. $t_{\alpha,df} = 1.7396$
   3. $t_{\beta,df} = 0.8633$
   4. new $n = [(t_{\alpha,df} + t_{\beta,df})^2 \cdot (CV/\Delta)]^2 =$ $(1.7396+0.8633)^2 \times (-0.2/0.1719)^2 = 9.1711$
4. Continue with n=9.1711/sequence (N=18.3422 → 19)
   1. df = 17.342; roundup to the next integer 18
   2. $t_{\alpha,df} = 1.7341$
   3. $t_{\beta,df} = 0.8620$
   4. new $n = [(t_{\alpha,df} + t_{\beta,df})^2 \cdot (CV/\Delta)]^2 =$ $(1.7341+0.8620)^2 \times (-0.2/0.1719)^2 = 9.1233$
5. Convergence reached (N=18.2466 → 19):
   Use 10 subjects/sequence (20 total)

S-C Chow and H Wang (2001)

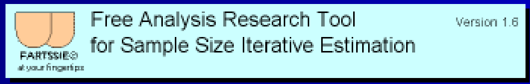
Patient's risk α 0.05, Power 80% (Producer's risk β 0.2), AR [0.80 – 1.25], CV 0.2 (20%), T/R 0.95

1. $\Delta = \ln(T/R) - \ln(1.25) = 0.1719$
2. Start with e.g. n=8/sequence
   1. $df_\alpha = \text{roundup}(2 \cdot n - 2) \cdot 2 - 2 = (2 \times 8 - 2) \times 2 - 2 = 26$
   2. $df_\beta = \text{roundup}(4 \cdot n - 2) = 4 \times 8 - 2 = 30$
   3. $t_{\alpha,df} = 1.7056$
   4. $t_{\beta/2,df} = 0.8538$
   5. new $n = \beta^2 \cdot [(t_{\alpha,df} + t_{\beta/2,df})^2/\Delta^2 =$ $0.2^2 \times (1.7056+0.8538)^2 / 0.1719^2 = 8.8723$
3. Continue with n=8.8723/sequence (N=17.7446 → 18)
   1. $df_\alpha = \text{roundup}(2 \cdot n - 2) \cdot 2 - 2 = (2 \times 8.8723 - 2) \times 2 - 2 = 30$
   2. $df_\beta = \text{roundup}(4 \cdot n - 2) = 4 \times 8.8723 - 2 = 34$
   3. $t_{\alpha,df} = 1.6973$
   4. $t_{\beta/2,df} = 0.8523$
   5. new $n = \beta^2 \cdot [(t_{\alpha,df} + t_{\beta/2,df})^2/\Delta^2 =$ $0.2^2 \times (1.6973+0.8538)^2 / 0.1719^2 = 8.8045$
4. Convergence reached (N=17.6090 → 18):
   Use 9 subjects/sequence (18 total)

sample size	18	19	20
power %	79.124	81.428	83.468

Approximations obsolete

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



http://individual.utoronto.ca/ddubins/FARTSSIE17.xls

or R / S+ →

```
alpha    <- 0.05     # alpha
CV       <- 0.30     # intra-subject CV
theta1   <- 0.80     # lower acceptance limit
theta2   <- 1/theta1 # upper acceptance limit
ratio    <- 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(ratio)-log(theta1))/s
  nc2    <- sqrt(n)*(log(ratio)-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")
```

- 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, logscale = TRUE,
  theta1 = 0.80, diff = 0.95, CV = 0.30,
  design = "2x2", exact = TRUE)
```

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

nQuery Advisor - [MTE2co-1.nqa]

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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*

```
require(PowerTost)
sampleN.TOST(alpha = 0.05, targetpower = 0.9, logscale = TRUE,
             theta1 = 0.8, theta2 = 1.25, theta0 = 0.95, CV = 0.2,
             design = "2x2", exact = TRUE, 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 calculate Power for a given sample size, use function *power.TOST*

```
require(PowerTost)
power.TOST(alpha=0.05, logscale=TRUE, theta1=0.8, theta2=1.25,
           theta0=0.95, CV=0.25, n=26, design="2x2", exact=TRUE)
[1] 0.7760553
power.TOST(alpha=0.05, logscale=TRUE, theta1=0.8, theta2=1.25,
           theta0=0.95, CV=0.20, n=22, design="2x2", exact=TRUE)
[1] 0.8688866
power.TOST(alpha=0.05, logscale=TRUE, theta1=0.8, theta2=1.25,
           theta0=0.95, CV=0.25, n=22, design="2x2", exact=TRUE)
[1] 0.6953401
power.TOST(alpha=0.05, logscale=TRUE, theta1=0.8, theta2=1.25,
           theta0=0.90, CV=0.20, n=26, design="2x2", exact=TRUE)
[1] 0.6694514
power.TOST(alpha=0.05, logscale=TRUE, theta1=0.8, theta2=1.25,
           theta0=0.90, CV=0.25, n=22, design="2x2", exact=TRUE)
[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)

Data from Pilot Studies

- Estimated CVs have a high degree of uncer-tainty (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

```
require(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.
  - A Sequential Design may also avoid an unnecessarily large pivotal 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.

Sample Size Calculations
…or the Myth of Power

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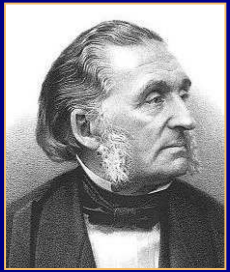
To bear in Remembrance...

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

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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 prospec-tive, not retrospective.

The fact that retrospective power adds no new infor-mation is harmless in its own right. However, in typical practice, it is used to exaggerate the validity of a signi-ficant 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

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