Package 'PowerTOST'

January 20, 2025

Encoding UTF-8

Type Package

Title Power and Sample Size for (Bio)Equivalence Studies

Version 1.5-6

Date 2024-03-18

Description Contains functions to calculate power and sample size for various study designs used in bioequivalence studies. Use known.designs() to see the designs supported. Power and sample size can be obtained based on different methods, amongst them prominently the TOST procedure (two one-sided t-tests). See README and NEWS for further information.

Imports mvtnorm, stats, utils, graphics, grDevices, cubature (>= 1.3-6)

Suggests crossdes, knitr, rmarkdown, tufte, emmeans

ByteCompile yes

LazyData true

VignetteBuilder knitr

URL <https://github.com/Detlew/PowerTOST>

BugReports <https://github.com/Detlew/PowerTOST/issues>

License GPL (>= 2)

NeedsCompilation no

Author Detlew Labes [aut, cre] (<<https://orcid.org/0000-0003-2169-426X>>),
Helmut Schütz [aut] (<<https://orcid.org/0000-0002-1167-7880>>),
Benjamin Lang [aut]

Maintainer Detlew Labes <DetlewLabes@gmx.de>

Repository CRAN

Date/Publication 2024-03-18 19:20:05 UTC

Contents

---

bib.CL   *Design matrices of period balanced incomplete block designs*

Description

This function returns the 'design' matrix of incomplete block designs described by Chow & Liu. The design matrices were recoded 1=R, 2=T1, 3=T2, . . .

Usage

```
bib.CL(trt, p)
```

Arguments

trt   Number of treatments (3 to 5).

p   Number of periods (2 to trt-1).

Value

Matrix containing the sequences in rows and periods in columns.
The entry (i, j) of the matrix corresponds to the treatment or dose (index) a subject within *i*-th sequence gets in the *j*-th period.

Author(s)

D. Labes

References

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3rd edition 2009. Chapter 2.6.

Examples

```
# 4 treatments/doses, 3 periods
bib.CL(4, 3)
# gives 4 sequences
# to see this in Chow & Liu's coding
tmt <- c("R", "T1", "T2", "T3")
matrix(tmt[bib.CL(4, 3)], ncol=3)
```

CI.BE   *1–2*alpha confidence interval given point estimate, CV, and n*

Description

Utility function to calculate the $1 - 2\alpha$ CI given point estimate, CV, and n for the various designs covered in this package.

Usage

```
CI.BE(alpha = 0.05, pe, CV, n, design = "2x2", robust = FALSE)
```

Arguments

alpha	Type I error probability, significance level. Defaults to 0.05.
pe	Point estimate (GMR).
CV	Coefficient of variation as ratio (not percent).
n	Total number of subjects if a scalar is given. Number of subjects in (sequence) groups if given as vector.
design	Character string describing the study's design. See known.designs() for designs covered in this package.
robust	Defaults to FALSE. Setting to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as n-seq. See known.designs()$df2 for designs covered in this package.

Value

Returns the $1 - 2\alpha$ confidence interval.
Returns a vector with named elements lower, upper if arguments pe and CV are scalars, else a matrix with columns lower, upper is returned.

Note

The function assumes an evaluation using log-transformed data.
The function assumes equal variances in case of design="parallel" and the higher order crossover designs.
The implemented formula covers balanced and unbalanced designs.

Whether the function vectorizes properly is not thoroughly tested.

Author(s)

D. Labes

Examples

```
# 90% confidence interval for the 2x2 crossover
# n(total) = 24
CI.BE(pe = 0.95, CV = 0.3, n = 24)
# should give
#    lower    upper
# 0.8213465 1.0988055
# same total number but unequal sequences
CI.BE(pe = 0.95, CV = 0.3, n = c(13, 11))
#    lower    upper
# 0.8209294 1.0993637
```

CI.RatioF   *1–2*alpha Fieller CI given point estimate, CV (, CVb) and n*

Description

Utility function to calculate the $1 - 2\alpha$ Fieller confidence interval given the point estimate, CV (, CVb), and n for the parallel group and 2×2 crossover.

Usage

```
CI.RatioF(alpha = 0.025, pe, CV, CVb, n, design = c("2x2", "parallel"))
```

Arguments

alpha	Type I error probability, aka significance level. Defaults here to 0.025 because this function is intended for studies with clinical endpoints.
pe	Point estimate of T/R ratio.
CV	Coefficient of variation as ratio (not percent). In case of design="parallel" this is the CV of the total variability, in case of design="2x2" the intra-subject CV.
CVb	CV of the between-subject variability. Only necessary for design="2x2".

n	Total number of subjects if a scalar is given.
	Number of subjects in (sequence) groups if given as vector.
design	A character string describing the study design.
	design="parallel" or design="2x2" allowed for a parallel two-group design or a classical TR|RT crossover design.

Details

The CV(within) and CVb(etween) in case of design="2x2" are obtainedvia an appropriate ANOVA from the error term and from the difference (MS(subject within sequence)-MS(error))/2.

Value

Returns the $1 - 2\alpha$ confidence interval.

Note

The function assumes an evaluation using un-transformed data.
The function assumes equal variances in case of design="parallel".
The formula implemented covers balanced and unbalanced designs.

Note that when the mean of the denominator of the ratio is close to zero, confidence intervals might be degenerated and are returned as NA. In such a case a warning is issued.

Whether the function vectorizes properly is not thoroughly tested.

This function is intended for studies with clinical endpoints. In such studies the 95% confidence intervals are usually used for equivalence testing. Therefore, alpha defaults here to 0.025 (see EMA 2000).

Author(s)

D. Labes

References

Locke CS. *An exact confidence interval from untransformed data for the ratio of two formulation means.* J Pharmacokin Biopharm. 1984;12(6):649–55. doi:10.1007/BF01059558

Hauschke D, Steinijans VW, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: John Wiley; 2007. Chapter 10. doi:10.1002/9780470094778.fmatter

European Medicines Agency, Committee for Proprietary Medicinal Products. *Points to consider on switching between superiority and non-inferiority.* London, 27 July 2000. CPMP/EWP/482/99

See Also

CI.BE, power.RatioF

Examples

```
# 95% Fieller CI for the 2x2 crossover
CI.RatioF(pe = 0.95, CV = 0.3, CVb = 0.6, n = 32)
```

---

ct5.1+ct5.2+ct5.3+ct5.4.1

Sample Size Tables for the Classical 2x2 Crossover Design

Description

These data.frames give sample size tables calculated with sampleN.TOST() for the 2×2 design.

Details

The data.frames can be accessed by their names.

data.frame	Description
ct5.1	Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1), exact
ct5.2	Multiplicative model, theta1=0.75, theta2=1.3333 (1/theta1), exact
ct5.3	Multiplicative model, theta1=0.9, theta2=1.1111 (1/theta1), exact
ct5.4.1	Additive model, theta1=–0.2, theta2=+0.2 (BE limits 0.80 – 1.20), exact

Note

Scripts for creation of these data.frames can be found in the /tests sub-directory of the package. Comparing the results of these scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST

Source

data.frame	Origin	Details
ct5.1	Hauschke *et al.*	Table 5.1 (p 113–114)
ct5.2	Hauschke *et al.*	Table 5.2 (p 115–116)
ct5.3	Hauschke *et al.*	Table 5.3 (p 118)
ct5.4.1	Chow & Liu	Table 5.4.1 (p 158)

References

Hauschke D, Steinijans VW, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: John Wiley; 2007.

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3rd edition 2009.

Examples

```
ct5.1
ct5.2
ct5.3
ct5.4.1
```

---

ct9.6.2+ct9.6.6   *Sample Size Tables for the 2x2x3 Replicate Crossover Design*

Description

These data.frames give sample size tables calculated with `sampleN.TOST()` for the 2×2×3 replicate crossover design (2-treatment 2-sequence 3-period design.

Details

The data.frames can be accessed by their names.

data.frame	Description
ct9.6.2	Additive model, theta1=–0.2, theta2=+0.2 (BE limits 0.80 – 1.20)
	approximate power via shifted non-central *t*-distribution
ct9.6.6	Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1)
	approximate power via shifted non-central *t*-distribution

Attention! CV is se (standard error) of residuals.

Note

Scripts for creation of these data.frames can be found in the `/tests` sub-directory of the package. Comparing the results of these scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST

Source

data.frame	Origin	Details
ct9.6.2	Chow & Liu	Table 9.6.2 (p 292)
ct9.6.6	Chow & Liu	Table 9.6.6 (p 293)

References

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3rd edition 2009.

Examples

```
ct9.6.2
ct9.6.6
```

---

ct9.6.4+ct9.6.8   *Sample Size Tables for the 2x4x4 Replicate Crossover Design*

Description

These data.frames give sample size tables calculated with sampleN.TOST() for the 2×4×4 replicate crossover design (2-treatment 4-sequence 4-period design).

Details

The data.frames can be accessed by their names.

data.frame	Description
ct9.6.4	Additive model, theta1=–0.2, theta2=+0.2 (BE limits 0.80 – 1.20)
	approximate power via shifted non-central *t*-distribution
ct9.6.8	Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1)
	approximate power via shifted non-central *t*-distribution

Attention! CV is se (standard error) of residuals.

Note

Scripts for creation of these data.frames can be found in the /tests sub-directory of the package. Comparing the results of these scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST

Source

data.frame	Origin	Details
ct9.6.4	Chow & Liu	Table 9.6.4 (p 294)
ct9.6.8	Chow & Liu	Table 9.6.8 (p 298)

References

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3rd edition 2009.

Examples

```
ct9.6.4
ct9.6.8
```

---

ctSJ.VIII.10+ctSJ.VIII.20+ctCW.III

Sample Size Tables for the Parallel Group Design

Description

These data.frames give sample size tables calculated with sampleN.TOST() for the parallel group design (2 groups).

Details

The data.frames can be accessed by their names.

data.frame	Description
ctSJ.VIII.10	Multiplicative model, theta1=0.9, theta2=1.1111 (1/theta1), target power=90% approximate power via non-central *t*-distribution
ctSJ.VIII.20	Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1), target power=90% approximate power via non-central *t*-distribution
ctCW.III	Additive model, theta1=–0.2, theta2=+0.2 (BE limits 0.80 – 1.20), exact

Attention! Julious gives sample size per group.

Note

Scripts for creation of these data.frames can be found in the /tests sub-directory of the package. Comparing the results of these scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST

Source

data.frame	Origin	Details
ctSJ.VIII.10	Julious	Table VIII (p. 1972), column 'Level of bioequivalence 10%'
ctSJ.VIII.20	Julious	Table VIII (p. 1972), column 'Level of bioequivalence 20%'
ctCW.III	Chow & Wang	Table III (p. 164)

Seems the last reference is not very reliable (compare to the table in the paper).

References

Julious SA. *Tutorial in Biostatistics. Sample sizes for clinical trials with Normal data.* Stat Med. 2004;23(12):1921–86. doi:10.1002/sim.1783

Chow SC, Wang H. *On Sample Size Calculation in Bioequivalence Trials.* J Pharmacokinet Pharmacodyn. 2001;28(2):155–69. doi:10.1023/A:1011503032353

Examples

```
ctSJ.VIII.10
ctSJ.VIII.20
ctCW.III
```

CV2se+se2CV+CV2mse+mse2CV

Helper functions

Description

Calculates the standard error or the mean squared error from a given CV and vice versa for lognormal data.

Usage

```
CV2se(CV)
se2CV(se)
CV2mse(CV)
mse2CV(mse)
```

Arguments

CV	coefficient of variatio as ratio (not percent)
se	standard error
mse	mean squared error (aka residual variance)

Value

```
Returns
se  = sqrt(log(CV^2+1))
CV  = sqrt(exp(se^2)-1)
mse = log(CV^2+1)
CV  = sqrt(exp(mse)-1)
```

Note

These functions were originally intended for internal use only but may be useful for others.

Author(s)

D. Labes

Examples

```
# these functions are one liners:
CV2se <- function(CV) return(sqrt(log(1.0 + CV^2)))
se2CV <- function(se) return(sqrt(exp(se^2)-1))

CV2se(0.3)
# should give:
# [1] 0.2935604

se2CV(0.2935604)
# [1] 0.3
```

CVCL   *Confidence limits of a CV for log-normal data*

Description

The function calculates the $1-\alpha$ confidence limits (either 1-sided or 2-sided) via the χ^2 distribution of the error variance the CV is based on.

Usage

```
CVCL(CV, df, side = c("upper", "lower", "2-sided"), alpha = 0.05)
```

Arguments

CV	Coefficient of variation as ratio (not percent)
df	degrees of freedom of the CV (error variance)
side	Side(s) to calculate the confidence limits for, defaults to upper
alpha	Type I error probability, aka significance level

Value

Numeric vector of the confidence limits named as `lower CL` and `upper CL`.
In case of the one-sided upper confidence limit the `lower CL` is = 0.
In case of the one-sided lower confidence limit the `upper CL` is = Inf.

Author(s)

D. Labes

Examples

```
# upper one-sided 95% CL of a CV=0.3
# from a study with df=22 (f.i. a 2x2 crossover with n=24)
# default side="upper" since not explicitly given
CVCL(0.3, df = 22)
# should give:
#  lower CL  upper CL
# 0.0000000 0.4075525
```

CVfromCI	*CV from a given Confidence interval*

Description

Calculates the CV (coefficient of variation) from a known confidence interval of a BE study.
Useful if no CV but the 90% CI was given in literature.

Usage

```
CVfromCI(pe, lower, upper, n, design = "2x2", alpha = 0.05, robust = FALSE)
CI2CV(pe, lower, upper, n, design = "2x2", alpha = 0.05, robust = FALSE)
```

Arguments

pe	Point estimate of the T/R ratio. The pe may be missing. In that case it will be calculated as geometric mean of `lower` and `upper`.
lower	Lower confidence limit of the BE ratio.
upper	Upper confidence limit of the BE ratio.
n	Total number of subjects under study if given as scalar. Number of subjects in (sequence) groups if given as vector.
design	Character string describing the study design. See `known.designs()` for designs covered in this package.
alpha	Error probability. Set it to (1-confidence)/2 (*i.e.* to 0.05 for the usual 90% confidence intervals).

robust   With robust=FALSE (the default) usual degrees of freedom of the designs are
                       used.
                       With robust=TRUE the degrees of freedom for the so-called robust evaluation
                       (df2 in known.designs()) will be used. This may be helpful if the CI was evalu-
                       ated via a mixed model or via intra-subject contrasts (aka Senn's basic estima-
                       tor).

Details

See Helmut Schütz' presentation for the algebra underlying this function.

Value

Numeric value of the CV as ratio.

Note

The calculations are based on the assumption of evaluation via log-transformed values.
The calculations are further based on a common variance of Test and Reference treatments in repli-
cate crossover studies or parallel group study, respectively.

In case of argument n given as n(total) and is not divisible by the number of (sequence) groups
the total sample size is partitioned to the (sequence) groups to have small imbalance only. A mes-
sage is given in such cases.
The estimated CV is conservative (*i.e.*, higher than actually observed) in case of unbalancedness.

CI2CV() is simply an alias to CVfromCI().

Author(s)

Original by D. Labes with suggestions by H. Schütz.
Reworked and adapted to unbalanced studies by B. Lang.

References

Yuan J, Tong T, Tang M-L. *Sample Size Calculation for Bioequivalence Studies Assessing Drug Ef-
fect and Food Effect at the Same Time With a 3-Treatment Williams Design.* Regul Sci. 2013;47(2):242–
7. doi:10.1177/2168479012474273

Examples

```
# Given a 90% confidence interval (without point estimate)
# from a classical 2x2 crossover with 22 subjects
CVfromCI(lower=0.91, upper=1.15, n=22, design="2x2")
# will give [1] 0.2279405, i.e a CV ~ 23%
#
# unbalanced 2x2 crossover study, but not reported as  such
CI2CV(lower=0.89, upper=1.15, n=24)
# will give a CV ~ 26.3%
# unbalancedness accounted for
CI2CV(lower=0.89, upper=1.15, n=c(16,8))
```

```
# should give CV ~ 24.7%
```

CVp2CV   *Decompose CV(T) and CV(R) from 'pooled' CV of T/R*

Description

Helper function to calculate CV(T) and CV(R) from a pooled CV(T/R) assuming a ratio of the intra-subject variances.

Usage

```
CVp2CV(CV, ratio = 1.5)
```

Arguments

CV   'pooled' CV of T and R (as ratio, not percent).

ratio   Ratio of the intra-subject variances s^2(T)/s^2(R).
                May be a vector.

Details

In case of knowing only the CV(T/R) f.i. from an ordinary cross-over you can calculate the components CV(T) and CV(R) assuming a ratio of the intra-subject variances.
The formula the function is based on:
`log(1.0 + CV^2) = (sWT^2 + sWR^2)/2`
Insert `sWT^2 = ratio * sWR^2` and solve for `sWR^2`.

Value

Returns a numeric vector of the CV values for Test and Reference if only one ratio is given.
Returns a matrix with named columns `CVwT` and `CVwR` if ratio is given as vector.

Author(s)

D. Labes

Examples

```
CVp2CV(0.4, ratio=2)
# gives
# [1] 0.4677952 0.3225018
```

CVpooled   *Pooled CV from several studies*

Description

This function pools CVs of several studies.

Usage

```
CVpooled(CVdata, alpha = 0.2, logscale = TRUE, robust = FALSE)
## S3 method for class 'CVp'
print(x, digits = 4, verbose = FALSE, ...)
```

Arguments

CVdata	A data.frame that must contain the columns CV, n and design where CV are the error CVs from the studies, n the number of subjects and design is a character string describing the study design. See known.designs() for designs covered in this package. If the design column is missing the classical 2×2 crossover is assumed for each study. A message is displayed under that circumstances. A data.frame that contains the columns CV and giving the degrees of freedom df directly is also accepted as CVdata.
alpha	Error probability for calculating an upper confidence limit of the pooled CV. Recommended 0.2–0.25 for use in subsequent sample size estimation. See f.i one of H. Schütz' presentations.
logscale	Should the calculations be done for log-transformed data? Defaults to TRUE.
robust	Defaults to FALSE. Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn' basic estimator). These dfs are calculated as n-seq. They are also often more appropriate if the CV comes from a 'true' mixed effects model evaluation (FDA model for average bioequivalence). See known.designs()\$df2 for the designs covered in this package.
x	An object of class "CVp".
digits	Number of significant digits for the CV and the CL.
verbose	Defaults to FALSE. Prints only the pooled CV and df. If set to TRUE the upper confidence limit is also printed.
...	More args to print(). None used.

Details

The pooled CV is obtained from the weighted average of the error variances obtained from the CVs of the single studies, weights are the degrees of freedom df.
If only n is given in the input CVdata, the dfs are calculated via the formulas given in known.designs().

If both n and df are given the df column precedes.

If `logscale=TRUE` the error variances are obtained via function `CV2se()`. Otherwise the pooled CV is obtained via pooling the CV^2.

Value

A list of class `"CVp"` with components

CV	value of the pooled CV
df	pooled degrees of freedom
CVupper	upper confidence interval of the pooled CV
alpha	input value

The class `"CVp"` has a S3 methods `print.CVp`.

Warning

Pooling of CVs from parallel group and crossover designs does not make any sense.
Also the function *does not* throw an error if you do so.

Note

The calculations for `logscale=FALSE` are not described in the references. They are implemented by analogy to the case via log-transformed data.
The calculations are based on a common variance of Test and Reference formulations in replicate crossover studies or a parallel group study, respectively.

Author(s)

D. Labes

References

H. Schütz' presentations about sample size challenges.

Patterson S, Jones B. *Bioequivalence and Statistics in Clinical Pharmacology.* Boca Raton: Chapman & Hall / CRC Press; 2nd edition 2017. Chapter 5.7 "Determining Trial Size".

See Also

known.designs, CVfromCI

Examples

```
# some data:
# the values for AUC, study 1 and study 2 are Example 3 of H. Schuetz' presentation
CVs <- ("
 PKmetric | CV   |  n |design| source
    AUC   | 0.20 | 24 | 2x2  | study 1
    Cmax  | 0.25 | 24 | 2x2  | study 1
```

```
    AUC   | 0.30 | 12 | 2x2  | study 2
    Cmax  | 0.31 | 12 | 2x2  | study 2
    AUC   | 0.25 | 12 | 2x2x4| study 3 (full replicate)
")
txtcon <- textConnection(CVs)
CVdata <- read.table(txtcon, header = TRUE, sep = "|",
                     strip.white = TRUE, as.is = TRUE)
close(txtcon)

# evaluation of the AUC CVs
CVsAUC <- subset(CVdata, PKmetric == "AUC")
CVpooled(CVsAUC, alpha = 0.2, logscale = TRUE)
# df of the 'robust' evaluation
CVpooled(CVsAUC, alpha = 0.2, logscale = TRUE, robust = TRUE)
# print also the upper CL, data example 3
CVsAUC3 <- subset(CVsAUC,design != "2x2x4")
print(CVpooled(CVsAUC3, alpha = 0.2, robust = TRUE), digits = 3, verbose = TRUE)
# will give the output:
# Pooled CV = 0.235 with 32 degrees of freedom (robust dfs)
# Upper 80% confidence limit of CV = 0.266
#
# Combining CVs from studies evaluated by ANOVA (robust=FALSE) and
# by a mixed effects model (robust=TRUE). dfs have to be provided!
CVs <- ("
  CV    | n  |design| source   | model | df
  0.212 | 24 | 2x2  | study 1  | fixed | 22
  0.157 | 27 | 3x3  | study 2  | fixed | 50
  0.148 | 27 | 3x3  | study 3  | mixed | 24
")
txtcon <- textConnection(CVs)
CVdata <- read.table(txtcon, header = TRUE, sep = "|",
                     strip.white = TRUE, as.is = TRUE)
close(txtcon)
print(CVpooled(CVdata, alpha = 0.2), digits = 3, verbose = TRUE)
# will give the output:
# Pooled CV = 0.169 with 96 degrees of freedom
# Upper 80% confidence limit of CV = 0.181
```

CVwRfromU   *CVwR from the upper expanded limit (ABEL)*

Description

Calculates the intra-subject CV (coefficient of variation) of the reference from the upper expanded limit of a BE study (replicate design for ABEL). Useful if no CV_{wR} but the expanded limits were given.

Usage

```
CVwRfromU(U, regulator = "EMA")
U2CVwR(U, regulator = "EMA")
```

Arguments

U	Upper expanded limit. Must be within {1.2500, 1.4319} if `regulator="EMA"` and within {1.2500, 1.5000} if `regulator="HC"`.
regulator	Regulatory body's settings for expanding the BE acceptance limits, given as a string from the choices `"EMA"` or `"HC"`. Defaults to `regulator="EMA"`.

Details

Only the upper expanded limit is supported since it offers one more significant digit than the lower expanded limit.

Value

Numeric value of the CVwR as ratio, where `CVwR = sqrt(exp((log(U)/r_const)^2)-1)`.

Note

`U2CVwR()` is simply an alias to `CVwRfromU()`.

Author(s)

H. Schütz

Examples

```
# Given the upper expanded limit and using the defaults
CVwRfromU(U = 1.38)
# should give [1] 0.44355, i.e., a CVwR ~ 44%
# Upper limit from a study according the Health Canada's rules
CVwRfromU(U = 1.48, regulator = "HC")
# should give [1] 0.55214
```

---

defunct   *Removed functions in PowerTOST*

Description

Details about removed functions in PowerTOST.

Details

`type1error.2TOST` was designed to calculate the type I error (*TIE*) rate of two simultaneous TOST procedures with some specified correlation of the parameters. It suffered from poor precision to obtain the *TIE* via simulations.

Due to the intersection-union principle the *TIE* is always upper bounded to α by theory and hence, `type1error.2TOST` was removed in version 1.4-7.

power.scABEL2 and sampleN.scABEL2 were deprecated in version 1.4-1. In power.scABEL and sampleN.scABEL the regulator component "est_method" is used for switching between simulations based on the EMA's ANOVA evaluation or ISC evaluation, respectively. power.scABEL2 and sampleN.scABEL2 were removed in version 1.4-3.

power2.TOST was deprecated in version 1.2-6 since power.TOST was modified in order to handle unbalanced sequences. power2.TOST was removed in version in version 1.2-7.

The functions power.NTIDFDA, sampleN.NTIDFDA and pa.NTIDFDA were deprecated in version 1.5-4 and were removed in version 1.5-6.

References

Berger RL, Hsu JC. *Bioequivalence Trials, Intersection-Union Tests and Equivalence Confidence Sets.* Stat Sci. 1996;11(4):283–302. JSTOR:2246021

See Also

power.TOST, power.scABEL, sampleN.scABEL, power.NTID, sampleN.NTID, and pa.NTID for the new functions.

---

deprecated   *Deprecated functions in PowerTOST*

Description

Details about deprecated functions in PowerTOST.

Details

The functions power.NTIDFDA, sampleN.NTIDFDA, and pa.NTIDFDA were deprecated in version 1.5-4.

See Also

power.NTID, sampleN.NTID, pa.NTID for the new functions.

exppower.noninf   *Expected power of the non-inferiority test*

Description

Calculates the so-called expected, *i.e.*, unconditional, power for a variety of study designs used in bioequivalence studies.

Usage

```
exppower.noninf(alpha = 0.025, logscale = TRUE, theta0, margin, CV, n,
                design = "2x2", robust = FALSE,
                prior.type = c("CV", "theta0", "both"), prior.parm = list(),
                method = c("exact", "approx"))
```

Arguments

alpha	Significance level (one-sided). Defaults here to 0.025.
logscale	Should the data be used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	Assumed 'true' (or 'observed' in case of prior.type != "CV") ratio or difference. In case of logscale=TRUE it must be given as ratio T/R. If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of margin and CV need also be given relative to the reference mean (specified as ratio). Defaults to 0.95 if logscale=TRUE or to -0.05 if logscale=FALSE
margin	Non-inferiority margin. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV and theta0 need also be given relative to the reference mean (specified as ratio). Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
CV	In case of logscale=TRUE the (geometric) coefficient of variation given as ratio. If logscale=FALSE the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of theta0, theta1 and theta2 need also be given relative to the reference mean (specified as ratio). In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.

n	Number of subjects under study.
	Is total number if given as scalar, else number of subjects in the (sequence) groups. In the latter case the length of n has to be equal to the number of (sequence) groups.
design	Character string describing the study design. See known.designs() for designs covered in this package.
robust	Defaults to FALSE. Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as n-seq.
	See known.designs()$df2 for designs covered in this package.
prior.type	Specifies which parameter uncertainty should be accounted for. In case of prior.type = "CV" (the default), only the uncertainty with respect to the CV will be considered (i.e. the given treatment effect is assumed to be fix). In case of prior.type = "theta0" only uncertainty with respect to the treatment ratio/difference will be accounted for (i.e. the given CV is assumed to be fix). In case of prior.type = "both" the power value will be unconditional with respect to both the CV and theta0.
prior.parm	A list of parameters expressing the prior information about the variability and/or treatment effect. Possible components are df, SEM, m and design.
	For prior.type = "CV" the degrees of freedom from the prior trial are required. This information can be provided by specifying the single component df or the combination consisting of m and design.
	For prior.type = "theta0" the standard error of the treatment difference from the prior trial is required. This information can be provided by specifying the single component SEM or the combination consisting of m and design.
	For prior.type = "both" the degrees of freedom and the standard error of the treatment difference are required. This information can be provided by specifying the combination consisting of df and SEM or via the combination m and design.
	See 'Details' for a technical description on each component.
method	Defaults to method="exact". In that case the expected power will be calculated as expected value of the power with respect to the (prior) distribution of the respective parameter(s).
	Set to method="approx" the expected power according to the approximate formulas given in the book from Julious or in the Julious/Owen paper will be calculated (using non-central *t*); this only affects prior.type = "CV".

Details

This function calculates the so-called expected power taking into account that usually the parameters (CV and/or theta0) are not known but *estimated* from a prior study with some uncertainty. The expected power is an unconditional power and can therefore be seen as probability for success. See references for further details.

The prior.parm argument is a list that can supply any of the following components:

df Error degrees of freedom from the prior trial (>4, maybe non-integer). df = Inf is allowed and for method = "exact" the result will then coincide with power.noninf(...).

Note: This corresponds to the df of both the CV and the difference of means.

SEM Standard error of the difference of means from the prior trial; must always be on additive scale (*i.e.*, usually log-scale).

m Number of subjects from prior trial. Specification is analogous to the main argument n.

design Study design of prior trial. Specification is analogous to the main argument design.

For prior.parm, the combination consisting of df and SEM requires a somewhat advanced knowledge of the prior trial (provided in the raw output from for example the software SAS, or may be obtained via [emmeans](#) of package emmeans. However, it has the advantage that if there were missing data the exact degrees of freedom and standard error of the difference can be used, the former possibly being non-integer valued (*e.g.* if the Kenward-Roger method was used).

Details on argument prior.type:

CV The expectation is calculated with respect to the Inverse-gamma distribution.

theta0 The expectation is calculated with respect to the conditional distribution theta0 | σ^2 = s^2 of the posteriori distribution of (theta0, σ^2) from the prior trial.

both The expectation is calculated with respect to the posteriori distribution of (theta0, σ^2) from the prior trial. Numerical calculation of the two-dimensional integral is performed via cubature::hcubature.

Notes on the underlying hypotheses
If the supplied margin is < 0 (logscale=FALSE) or < 1 (logscale=TRUE), then it is assumed higher response values are better. The hypotheses are
H0: theta0 <= margin vs. H1: theta0 > margin
where theta0 = mean(test)-mean(reference) if logscale=FALSE
or
H0: log(theta0) <= log(margin) vs. H1: log(theta0) > log(margin)
where theta0 = mean(test)/mean(reference) if logscale=TRUE.

If the supplied margin is > 0 (logscale=FALSE) or > 1 (logscale=TRUE), then it is assumed lower response values are better. The hypotheses are
H0: theta0 >= margin vs. H1: theta0 < margin
where theta0 = mean(test)-mean(reference) if logscale=FALSE
or
H0: log(theta0) >= log(margin) vs. H1: log(theta0) < log(margin)
where theta0 = mean(test)/mean(reference) if logscale=TRUE.
This latter case may also be considered as 'non-superiority'.

Value

Value of expected power according to the input.

Author(s)

B. Lang, D. Labes

References

Grieve AP. *Confidence Intervals and Sample Sizes.* Biometrics. 1991;47:1597–603. doi:10.2307/2532411

O'Hagan, Stevens, JW, Campell MJ. *Assurance in Clinical Trial Design.* Pharm Stat. 2005;4:187–201. doi:10.1002/pst.175

Julious SA, Owen RJ. *Sample size calculations for clinical studies allowing for uncertainty in variance.* Pharm Stat. 2006;5:29–37. doi:10.1002/pst.197

Julious SA. *Sample sizes for Clinical Trials.* Boca Raton: CRC Press / Chapman & Hall; 2010.

Bertsche A, Nehmitz G, Beyersmann J, Grieve AP. *The predictive distribution of the residual variability in the linear-fixed effects model for clinical cross-over trials.* Biom J. 2016;58(4):797–809. doi:10.1002/bimj.201500245

Box GEP, Tiao GC. *Bayesian Inference in Statistical Analysis.* Boston: Addison-Wesley; 1992.

Held L, Sabanes Bove D. *Applied Statistical Inference. Likelihood and Bayes.* Berlin, Heidelberg: Springer; 2014. doi:10.1007/9783642378874

Senn S. *Cross-over Trials in Clinical Research.* Chichester: John Wiley & Sons; 2nd edition 2002.

Zierhut ML, Bycott P, Gibbs MA, Smith BP, Vicini P. *Ignorance is not bliss: Statistical power is not probability of trial success.* Clin Pharmacol Ther. 2015;99:356–9. doi:10.1002/cpt.257

See Also

expsampleN.noninf, power.noninf

Examples

```
# Expected power for non-inferiority test for a 2x2 crossover
# with 40 subjects. CV 30% known from a pilot 2x2 study with
# 12 subjects
# using all the defaults for other parameters (theta0 carved in stone)
# should give: [1] 0.6761068
exppower.noninf(CV = 0.3, n = 40, prior.parm = list(df = 12-2))
# or equivalently
exppower.noninf(CV = 0.3, n = 40, prior.parm = list(m = 12, design = "2x2"))

# May be also calculated via exppower.TOST() after setting upper acceptance limit
# to Inf and alpha=0.025
exppower.TOST(CV = 0.3, n = 40, prior.parm = list(df = 10), theta2 = Inf, alpha=0.025)

# In contrast: Julious approximation
exppower.noninf(CV = 0.3, n = 40, prior.parm = list(df = 10), method = "approx")
# should give: [1] 0.6751358

# Compare this to the usual (conditional) power (CV known, "carved in stone")
power.noninf(CV = 0.3, n = 40)
# should give: [1] 0.7228685
# same as if setting df = Inf in function exppower.noninf()
exppower.noninf(CV = 0.3, n = 40, prior.parm = list(df = Inf))

# Expected power for a 2x2 crossover with 40 subjects
```

```
# CV 30% and theta0 = 0.95 known from a pilot 2x2 study with 12 subjects
# using uncertainty with respect to both CV and theta0
exppower.noninf(CV = 0.3, theta0 = 0.95, n = 40,
                prior.parm = list(m = 12, design = "2x2"), prior.type = "both")
# should give a decrease of expected power to 0.5982852
```

exppower.TOST	*Expected power of the TOST procedure*

Description

Calculates the so-called expected, *i.e.*, unconditional, power for a variety of study designs used in bioequivalence studies.

Usage

```
exppower.TOST(alpha = 0.05, logscale = TRUE, theta0, theta1, theta2,
              CV, n, design = "2x2", robust = FALSE,
              prior.type = c("CV", "theta0", "both"), prior.parm = list(),
              method = c("exact", "approx"))
```

Arguments

alpha	Significance level (one-sided). Commonly set to 0.05.
logscale	Should the data be used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	Assumed 'true' (or 'observed' in case of prior.type != "CV") ratio or difference. In case of logscale=TRUE it must be given as ratio T/R. If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of CV, theta1 and theta2 need also be given relative to the reference mean (specified as ratio). Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE
theta1	Lower (bio-)equivalence limit. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, theta0 and theta2 need also be given relative to the reference mean (specified as ratio). Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
theta2	Upper (bio-)equivalence limit. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former

case the units of CV, theta0 and theta1 need also be given relative to the reference mean (specified as ratio).

If not given, theta2 will be calculated as 1/theta1 if logscale=TRUE or as -theta1 if logscale=FALSE.

CV
In case of logscale=TRUE the (geometric) coefficient of variation given as ratio. If logscale=FALSE the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of theta0, theta1 and theta2 need also be given relative to the reference mean (specified as ratio).

In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.

n
Number of subjects under study.
Is total number if given as scalar, else number of subjects in the (sequence) groups. In the latter case the length of n has to be equal to the number of (sequence) groups.

design
Character string describing the study design. See [known.designs](#) for designs covered in this package.

robust
Defaults to FALSE. Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These df are calculated as n-seq.
See known.designs()$df2 for designs covered in this package.

prior.type
Specifies which parameter uncertainty should be accounted for. In case of prior.type = "CV" (the default), only the uncertainty with respect to the CV will be considered (i.e. the given treatment effect is assumed to be fix). In case of prior.type = "theta0" only uncertainty with respect to the treatment ratio/difference will be accounted for (i.e. the given CV is assumed to be fix). In case of prior.type = "both" the power value will be unconditional with respect to both the CV and theta0.

prior.parm
A list of parameters expressing the prior information about the variability and/or treatment effect. Possible components are df, SEM, m and design.
For prior.type = "CV" the degrees of freedom from the prior trial are required. This information can be provided by specifying the single component df or the combination consisting of m and design.
For prior.type = "theta0" the standard error of the treatment difference from the prior trial is required. This information can be provided by specifying the single component SEM or the combination consisting of m and design.
For prior.type = "both" the degrees of freedom and the standard error of the treatment difference are required. This information can be provided by specifying the combination consisting of df and SEM or via the combination m and design.
See 'Details' for a technical description on each component.

method
Defaults to method="exact". In that case the expected power will be calculated as expected value of the power with respect to the (prior) distribution of the respective parameter(s).

Set to `method="approx"` the expected power according to the approximate formulas given in the book from Julious or in the Julious/Owen paper will be calculated (using non-central *t*); this only affects `prior.type = "CV"`.

Details

This function calculates the so-called expected power taking into account that usually the parameters (CV and/or theta0) are not known but estimated from a prior study with some uncertainty. The expected power is an unconditional power and can therefore be seen as probability for success. See references for further details.

The `prior.parm` argument is a list that can supply any of the following components:

df Error degrees of freedom from the prior trial (>4, maybe non-integer). `df = Inf` is allowed and for `method = "exact"` the result will then coincide with `power.TOST(...)`.
  Note: This corresponds to the df of both the CV and the difference of means.

SEM Standard error of the difference of means from the prior trial; must always be on additive scale (*i.e.*, usually log-scale).

m Number of subjects from prior trial. Specification is analogous to the main argument `n`.

design Study design of prior trial. Specification is analogous to the main argument `design`.

For `prior.parm`, the combination consisting of df and SEM requires a somewhat advanced knowledge of the prior trial (provided in the raw output from for example the software SAS, or may be obtained via [emmeans](#) of package emmeans. However, it has the advantage that if there were missing data the exact degrees of freedom and standard error of the difference can be used, the former possibly being non-integer valued (*e.g.*, if the Kenward-Roger method was used).

Details on argument `prior.type`:

CV The expectation is calculated with respect to the Inverse-gamma distribution.

theta0 The expectation is calculated with respect to the conditional distribution theta0 | σ^2 = s^2 of the posteriori distribution of (theta0, σ^2) from the prior trial.

both The expectation is calculated with respect to the posteriori distribution of (theta0, σ^2) from the prior trial. Numerical calculation of the two-dimensional integral is performed via [hcubature](#).

Value

Value of expected power according to the input.

Author(s)

B. Lang (thanks to G. Nehmiz for the helpful discussions), D. Labes

References

Grieve AP. *Confidence Intervals and Sample Sizes.* Biometrics. 1991;47:1597–603. doi:10.2307/2532411

O'Hagan, Stevens, JW, Campell MJ. *Assurance in Clinical Trial Design.* Pharm Stat. 2005;4:187–201. doi:10.1002/pst.175

Julious SA, Owen RJ. *Sample size calculations for clinical studies allowing for uncertainty in variance.* Pharm Stat. 2006;5:29–37. doi:10.1002/pst.197

Julious SA. *Sample sizes for Clinical Trials.* Boca Raton: CRC Press / Chapman & Hall; 2010.

Bertsche A, Nehmitz G, Beyersmann J, Grieve AP. *The predictive distribution of the residual variability in the linear-fixed effects model for clinical cross-over trials.* Biom J. 2016;58(4):797–809. doi:10.1002/bimj.201500245

Box GEP, Tiao GC. *Bayesian Inference in Statistical Analysis.* Boston: Addison-Wesley; 1992.

Held L, Sabanes Bove D. *Applied Statistical Inference. Likelihood and Bayes.* Berlin, Heidelberg: Springer; 2014. doi:10.1007/9783642378874

Senn S. *Cross-over Trials in Clinical Research.* Chichester: John Wiley & Sons; 2nd edition 2002.

Zierhut ML, Bycott P, Gibbs MA, Smith BP, Vicini P. *Ignorance is not bliss: Statistical power is not probability of trial success.* Clin Pharmacol Ther. 2015;99:356–9. doi:10.1002/cpt.257

See Also

expsampleN.TOST, power.TOST

Examples

```
# Expected power for a 2x2 crossover with 40 subjects
# CV 30% known from a pilot 2x2 study with 12 subjects
# using all the defaults for other parameters (theta0 carved in stone)
exppower.TOST(CV = 0.3, n = 40, prior.parm = list(df = 12-2))
# should give: [1] 0.7365519
# or equivalently
exppower.TOST(CV = 0.3, n = 40, prior.parm = list(m = 12, design = "2x2"))

# In contrast: Julious approximation
exppower.TOST(CV = 0.3, n = 40, prior.parm = list(df = 10), method = "approx")
# should give: [1] 0.7359771

# Compare this to the usual (conditional) power (CV known, "carved in stone")
power.TOST(CV = 0.3, n = 40)
# should give: [1] 0.8158453
# same as if setting df = Inf in function exppower.TOST()
exppower.TOST(CV = 0.3, n = 40, prior.parm = list(df = Inf))

# Expected power for a 2x2 crossover with 40 subjects
# CV 30% and theta0 = 0.95 known from a pilot 2x2 study with 12 subjects
# using uncertainty with respect to both CV and theta0
exppower.TOST(CV = 0.3, theta0 = 0.95, n = 40,
              prior.parm = list(m = 12, design = "2x2"), prior.type = "both")
# should give [1] 0.5114685
```

---

expsampleN.noninf   *Sample size based on expected power for the non-inferiority test*

Description

Estimates the sample size based on the expected power for a variety of designs used in bioequivalence studies. See known.designs for the study designs covered.

Usage

```
expsampleN.noninf(alpha = 0.025, targetpower = 0.8, logscale = TRUE,
                  theta0, margin, CV, design = "2x2", robust = FALSE,
                  prior.type = c("CV", "theta0", "both"), prior.parm = list(),
                  method = c("exact", "approx"), print = TRUE, details)
```

Arguments

alpha	Significance level (one-sided). Defaults here to 0.025.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
logscale	Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.
theta0	Assumed 'true' (or 'observed' in case of prior.type != "CV") ratio or difference.
	In case of logscale=TRUE it must be given as ratio T/R.
	If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of margin and CV need also be given relative to the reference mean (specified as ratio).
	Defaults to 0.95 if logscale=TRUE or to -0.05 if logscale=FALSE
margin	Non-inferiority margin.
	In case of logscale=TRUE it is given as ratio.
	If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV and theta0 need also be given relative to the reference mean (specified as ratio).
	Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
CV	In case of logscale=TRUE the (geometric) coefficient of variation given as ratio. If logscale=FALSE the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of theta0, theta1 and theta2 need also be given relative to the reference mean (specified as ratio).

                If `prior.type="CV"` may be given as vector: The CVs are then pooled (as a weighted mean with their degrees of freedoms as weights).

                In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.

design	Character string describing the study design. See known.designs() for designs covered in this package.
robust	Defaults to FALSE. With that value the usual degrees of freedom will be used. Setting to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These df are calculated as n-seq. See known.designs() for designs covered in this package.
prior.type	Specifies which parameter uncertainty should be accounted for. In case of `prior.type="CV"` (the default), only the uncertainty with respect to the CV will be considered (*i.e.*, the given treatment effect is assumed to be fix). In case of `prior.type="theta0"` only uncertainty with respect to the treatment ratio/difference will be accounted for (*i.e.*, the given CV is assumed to be fix). In case of `prior.type="both"` the power value will be unconditional with respect to both the CV and theta0.
prior.parm	A list of parameters expressing the prior information about the variability and/or treatment effect. Possible components are df, SEM, m, design. For `prior.type="CV"` the degrees of freedom from the prior trial are required. This information can be provided by specifying the single componentdf or the combination consisting of m and design. For `prior.type = "theta0"` the standard error of the treatment difference from the prior trial is required. This information can be provided by specifying the single component SEM or the combination consisting of m and design. For `prior.type = "both"` the degrees of freedom and the standard error of the treatment difference are required. This information can be provided by specifying the combination consisting of df and SEM or via the combination m and design. See section 'Details' for a technical description of each component.
method	Defaults to method="exact". In that case the expected power will be calculated as expected value of the power with respect to the (prior) distribution of the respective parameter(s). Set to method="approx" the expected power according to the approximate formulas given by Julious or Julious & Owen will be calculated (using the non-central *t*); this only affects prior.type = "CV".
print	If TRUE (default) the function prints its results. If FALSE only a data.frame with the results will be returned.
details	If TRUE the design characteristics and the steps during sample size calculations will be shown. If not specified, the default value is FALSE for prior.type != "both" and TRUE otherwise.

Details

The sample size is estimated based on iterative evaluation of expected power. The starting value of the sample size search is taken from a large sample approximation if `prior.type="CV"`. Else an empirical start value is obtained. Note that in case of `prior.type="both"` the calculation may still take several seconds.

Note also that the expected power is always bounded above by the so-called probability of technical success (PTS) which may be a value less than 1.Therefore, it may be possible that it is either not possible to calculate the required sample size at all or that the sample size gets very large if the given targetpower is less but close to the PTS.

Notes on the underlying hypotheses

If the supplied margin is < 0 (`logscale=FALSE`) or < 1 (`logscale=TRUE`), then it is assumed *higher* response values are better. The hypotheses are
```
H0: theta0 <= margin
H1: theta0 >  margin
```
where theta0 = mean(test)-mean(reference) if `logscale=FALSE`
or
```
H0: log(theta0) <= log(margin)
H1: log(theta0) >  log(margin)
```
where theta0 = mean(test)/mean(reference) if `logscale=TRUE`.

If the supplied margin is > 0 (`logscale=FALSE`) or > 1 (`logscale=TRUE`), then it is assumed *lower* response values are better. The hypotheses are
```
H0: theta0 >= margin
H1: theta0 <  margin
```
where theta0 = mean(test)-mean(reference) if `logscale=FALSE`
or
```
H0: log(theta0) >= log(margin)
H1: log(theta0) <  log(margin)
```
where theta0 = mean(test)/mean(reference) if `logscale=TRUE`.
This latter case may also be considered as 'non-superiority'.

Value

A data.frame with the input values and the result of the sample size estimation.
The `Sample size` column contains the *total* sample size in case of all designs implemented.

Author(s)

B. Lang, D. Labes

References

Grieve AP. *Confidence Intervals and Sample Sizes.* Biometrics. 1991;47:1597–603. doi:10.2307/2532411

O'Hagan, Stevens, JW, Campell MJ. *Assurance in Clinical Trial Design.* Pharm Stat. 2005;4:187–201. doi:10.1002/pst.175

Julious SA, Owen RJ. *Sample size calculations for clinical studies allowing for uncertainty in variance.* Pharm Stat. 2006;5:29–37. doi:10.1002/pst.197

Julious SA. *Sample sizes for Clinical Trials.* Boca Raton: CRC Press; 2010.

Bertsche A, Nehmitz G, Beyersmann J, Grieve AP. *The predictive distribution of the residual variability in the linear-fixed effects model for clinical cross-over trials.* Biom J. 2016;58(4):797–809. doi:10.1002/bimj.201500245

Box GEP, Tiao GC. *Bayesian Inference in Statistical Analysis.* Boston: Addison-Wesley; 1992.

Held L, Sabanes Bove D. *Applied Statistical Inference. Likelihood and Bayes.* Berlin, Heidelberg: Springer; 2014. doi:10.1007/9783642378874

Senn S. *Cross-over Trials in Clinical Research.* Chichester: John Wiley & Sons; 2nd edition 2002.

Zierhut ML, Bycott P, Gibbs MA, Smith BP, Vicini P. *Ignorance is not bliss: Statistical power is not probability of trial success.* Clin Pharmacol Ther. 2015;99:356–9. doi:10.1002/cpt.257

See Also

exppower.noninf, known.designs, sampleN.noninf

Examples

```
# Classical 2x2 cross-over, target power = 80%,
# assumed true ratio = 95%, margin = 0.8,
# intra-subject CV=30% estimated from prior 2x2 trial
# with m = 12 subjects
expsampleN.noninf(theta0 = 0.95, margin = 0.8, CV = 0.3, design = "2x2",
                  prior.parm = list(m = 12, design = "2x2"))
# gives n = 58 with achieved expected power 0.809148
# Compare this to the usual sample size with CV assumed
# as 'carved in stone'
sampleN.noninf(theta0 = 0.95, margin = 0.8, CV = 0.3)

# Perform 'non-superiority' (lower is better) with assumed
# true ratio = 105% and margin 125%
expsampleN.noninf(theta0 = 1.05, margin = 1.25, CV = 0.3, design = "2x2",
                  prior.parm = list(m = 12, design = "2x2"))
# should give n = 56 with achieved expected power 0.806862

# More than one CV with corresponding degrees of freedom
# other settings as above in first example
CVs <- c(0.25, 0.3)
dfs <- c(22, 10)
expsampleN.noninf(theta0 = 0.95, margin = 0.8, CV = CVs,
                  prior.parm = list(df = dfs))
# should give a pooled CV=0.2664927 with 32 df and a sample
# size n=42 with achieved expected power 0.814073 exact
# achieved expected power 0.816163 approximate acc. to Julious

# Uncertainty is accounted for CV and theta0

expsampleN.noninf(CV = 0.3, prior.type = "both",
                  prior.parm = list(m = 12, design = "2x2"))
```

```
# gives a dramatic increase in sample size (n = 194)
# due to small pilot trial
```

---

expsampleN.TOST   *Sample size based on expected power*

Description

Estimates the sample size based on the expected power for a variety of study designs used in bioe-quivalence studies. See known.designs for the study designs covered.

Usage

```
expsampleN.TOST(alpha = 0.05, targetpower = 0.8, logscale=TRUE, theta0,
                theta1, theta2, CV, design = "2x2", robust = FALSE,
                prior.type = c("CV", "theta0", "both"), prior.parm = list(),
                method = c("exact", "approx"), print = TRUE, details)
```

Arguments

alpha	Significance level (one-sided). Commonly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
logscale	Should the data used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	Assumed 'true' (or 'observed' in case of prior.type != "CV") bioequivalence ratio or difference.
	In case of logscale=TRUE it must be given as ratio T/R.
	If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of CV, theta1 and theta2 need also be given relative to the reference mean (specified as ratio).
	Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE
theta1	Lower (bio-)equivalence limit.
	In case of logscale=TRUE it is given as ratio.
	If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, theta0 and theta2 need also be given relative to the reference mean (specified as ratio).
	Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
theta2	Upper (bio-)equivalence limit.
	In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, theta0 and theta1 need also be given relative to the reference mean (specified as ratio).

	If not given, theta2 will be calculated as 1/theta1 if logscale=TRUE or as -theta1 if logscale=FALSE.
CV	In case of logscale=TRUE the (geometric) coefficient of variation given as ratio. If logscale=FALSE the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of theta0, theta1 and theta2 need also be given relative to the reference mean (specified as ratio).
	If prior.type="CV" may be given as vector: The CVs are then pooled (as a weighted mean with their degrees of freedoms as weights).
	In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.
design	Character string describing the study design. See known.designs for designs covered in this package.
robust	Defaults to FALSE. With that value the usual degrees of freedom will be used. Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These df are calculated as n-seq. See known.designs()$df2 for designs covered in this package.
prior.type	Specifies which parameter uncertainty should be accounted for. In case of prior.type = "CV" (the default), only the uncertainty with respect to the CV will be considered (*i.e.*, the given treatment effect is assumed to be fix). In case of prior.type = "theta0" only uncertainty with respect to the treatment ratio/difference will be accounted for (*i.e.*, the given CV is assumed to be fix). In case of prior.type = "both" the power value will be unconditional with respect to both the CV and theta0.
prior.parm	A list of parameters expressing the prior information about the variability and/or treatment effect. Possible components are df, SEM, m, design. For prior.type = "CV" the degrees of freedom from the prior trial are required. This information can be provided by specifying the single component df or the combination consisting of m and design. For prior.type = "theta0" the standard error of the treatment difference from the prior trial is required. This information can be provided by specifying the single component SEM or the combination consisting of m and design. For prior.type = "both" the degrees of freedom and the standard error of the treatment difference are required. This information can be provided by specifying the combination consisting of df and SEM or via the combination m and design. See 'Details' for a technical description on each component.
method	Defaults to method="exact". In that case the expected power will be calculated as expected value of the power with respect to the (prior) distribution of the respective parameter(s). Set to method="approx" the expected power according to the approximate formulas given in the book from Julious or in the Julious/Owen paper will be calculated (using non-central *t*); this only affects prior.type = "CV".

print	If TRUE (default) the function prints its results. If FALSE only a data.frame with the results will be returned.
details	If TRUE the design characteristics and the steps during sample size calculations will be shown.
	If not specified, the default value is FALSE for prior.type != "both" and TRUE otherwise.

Details

The sample size is calculated based on iterative evaluation of expected power. The starting value of the sample size search is taken from a large sample approximation if prior.type = "CV". Otherwise, an empirical start value is obtained. Note that in case of prior.type = "both" the calculation may still take several seconds.

Note also that the expected power is always bounded above by the so-called probability of technical success (PTS) which may be a value less than 1. Therefore, it may be possible that it is either not possible to calculate the required sample size at all or that the sample size gets very large if the given targetpower is less but close to the PTS.

The estimated sample size gives always the *total* number of subjects (not subject/sequence in crossovers or subjects/group in parallel designs – like in some other software packages).

Value

A data.frame with the input values and the result of the sample size estimation.
The Sample size column contains the total sample size in case of all designs implemented.

Author(s)

B. Lang, D. Labes

References

Grieve AP. *Confidence Intervals and Sample Sizes.* Biometrics. 1991;47:1597–603. doi:10.2307/2532411

O'Hagan, Stevens, JW, Campell MJ. *Assurance in Clinical Trial Design.* Pharm Stat. 2005;4:187–201. doi:10.1002/pst.175

Julious SA, Owen RJ. *Sample size calculations for clinical studies allowing for uncertainty in variance.* Pharm Stat. 2006;5:29–37. doi:10.1002/pst.197

Julious SA. *Sample sizes for Clinical Trials.* Boca Raton: CRC Press / Chapman & Hall; 2010.

Bertsche A, Nehmitz G, Beyersmann J, Grieve AP. *The predictive distribution of the residual variability in the linear-fixed effects model for clinical cross-over trials.* Biom J. 2016;58(4):797–809. doi:10.1002/bimj.201500245

Box GEP, Tiao GC. *Bayesian Inference in Statistical Analysis.* Boston: Addison-Wesley; 1992.

Held L, Sabanes Bove D. *Applied Statistical Inference. Likelihood and Bayes.* Berlin, Heidelberg: Springer; 2014. doi:10.1007/9783642378874

Senn S. *Cross-over Trials in Clinical Research.* Chichester: John Wiley & Sons; 2nd edition 2002.

Zierhut ML, Bycott P, Gibbs MA, Smith BP, Vicini P. *Ignorance is not bliss: Statistical power is not probability of trial success.* Clin Pharmacol Ther. 2015;99:356–9. doi:10.1002/cpt.257

See Also

exppower.TOST, known.designs, sampleN.TOST

Examples

```
# Classical 2x2 cross-over, target power = 80%,
# BE limits 80 ... 125%, assumed true BE ratio = 95%,
# intra-subject CV=30% estimated from prior 2x2 trial
# with m = 30 subjects
expsampleN.TOST(CV=0.3, prior.parm = list(m = 30, design = "2x2"))
# -> gives n = 42 with achieved expected power 0.806262
# Compare this to the usual sample size with CV assumed known ('carved in stone')
sampleN.TOST(CV=0.3)
# -> gives n = 40 subjects
# Compare this to the case where uncertainty is accounted for CV and theta0
# Not run due to timing policy of CRAN - may run several seconds

expsampleN.TOST(CV=0.3, prior.parm = list(m = 30, design = "2x2"),
                prior.type = "both")
# -> gives n = 72 subjects

# More than one CV with corresponding degrees of freedom
# other settings as above in first example
CVs <- c(0.25, 0.3)
dfs <- c(22, 10)
expsampleN.TOST(CV=CVs, prior.parm = list(df = dfs))
# -> gives a pooled CV=0.2664927 with df=32
# and a sample size n=34 with achieved expected power 0.812653 exact
# achieved expected power 0.815019 approximate acc. Julious
```

---

known.designs   *Show the 'known' designs*

Description

Returns the known study designs for which power and sample size can be calculated within this package.

Usage

```
known.designs()
```

Details

This function is for informal purposes and used internally for obtaining characteristics of the designs used in calculation formulas.

Value

Returns a data.frame with

`no`	number of the design
`design`	character string for identifying the design
`df`	degrees of freedom of the design
`df2`	'robust' degrees of freedom of the design
`steps`	step width in the iterative sample size estimation
`bk`	so-called design constant in terms of total n
`bkni`	design constant in terms of number of subjects in (sequence) groups

The design character string has to be used in the functions calls for power and sample size.

Note

The design string for higher order crossover designs is named as:
`treatments x sequences x periods` in case of replicate designs and
`treatments x periods` in case of crossover designs for more then 2 treatments with number of sequences equal number of treatments.

The df for the replicate crossover designs are those without carry-over in the model.
Chen *et al.* used models with carry-over, *i.e.*, one df lower than here.

The design constant bk in case of design 2x2x4 is here bk=1.
Chen *et al.* used bk=1.1 due to carry-over in the model.

n is the **total** number of subjects for all designs implemented.
df2 = degrees of freedom for the so-called 'robust' analysis (aka Senn's basic estimator).
These degrees of freedom are often also more appropriate in case of evaluation via a 'true' mixed model (*e.g.* the FDA' for replicate designs).

The design `2x2x2r` is the 2-treatment-2-sequence-2-period design with 2 repeated targets determined in each period (sequences TT|RR or RR|TT) described by Liu. Implemented are the characteristics of this design for the evaluation via assuming no S×F interaction and equal variabilities of Test and Reference.

Author(s)

D. Labes

References

Chen KW, Chow SC, Liu G. *A Note on Sample Size Determination for Bioequivalence Studies with Higher-order Crossover Designs.* J Pharmacokin Biopharm. 1997;25(6):753–65.

Senn S. *Cross-over Trials in Clinical Research.* Chichester: John Wiley & Sons; 2nd edition 2002.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Guidance for Industry. Statistical Approaches to Establishing Bioequivalence.* January 2001. download

Liu J-p. *Use of the Repeated Crossover design in Assessing Bioequivalence.* Stat Med. 1995;14(9-10):1067–78.

Examples

```
known.designs()
```

OwensQ   *Owen's Q-function*

Description

Calculates Owen's Q function.

Usage

```
OwensQ(nu, t, delta, a=0, b)
```

Arguments

nu	degree of Owen's Q
t	parameter t
delta	parameter delta
a	lower integration limit, only a=0 implemented
b	upper integration limit

Details

Uses the relationship to non-central *t*-distribution (see Chou)

```
OwensQ = pt(t, df=nu, ncp=delta) - Integal_b_Inf(Q_integrand)
```

The definite integral is numerically evaluated using integrate after a variables transformation resulting in the integration range from 0 to 1 instead of the semi-infinite original range. This may result in higher precision and better numerical stability.

The arguments to the function must be scalars. No vectors allowed.

Value

Numeric value of Owen's Q-function at given input arguments.

Note

This function is intended for internal use in the power calculations.
But may be useful for others.

Author(s)

D. Labes

References

Owen DB. *A special case of a bivariate non-central t-distribution.* Biometrika. 1965;52(3/4):437–46. doi:10.2307/2333696

Chou YM. *A bivariate noncentral T-distibution with applications.* Commun Stat Theory Methods. 1992;21(12):3427–62. doi:10.1080/03610929208830988

See Also

OwensQQwen

Examples

```
# This function is mainly intended for internal use.
OwensQ(10, 2.5, 5, 0, 2)
#should give [1] 9.388137e-06
OwensQ(10, -2.5, -5, 0, 2)
#should give [1] 0.05264363
```

OwensQOwen   *Owen's Q-function via repeated integration by parts*

Description

This is an implementation of the algorithm given by Owen via repeated integration by parts.

Usage

```
OwensQOwen(nu, t, delta, a=0, b)
```

Arguments

nu	degree of Owen's Q
t	parameter t
delta	parameter delta
a	lower integration limit. Only a=0 implemented, other values give an error.
b	upper integration limit

Value

Numeric value of Owen's Q function.

Note

The argument a=0 could be dropped but is retained for sake of completeness.

Note

This function is mainly for comparative / validation purposes.
The function requireds OwensT function.

Author(s)

D. Labes

References

Owen DB. *A special case of a bivariate non-central t-distribution.* Biometrika. 1965;52(3/4):437–
46. doi:10.2307/2333696

See Also

OwensQ, OwensT

Examples

```
# comparison of the results of both implementations
# both should give [1] 0.0731726
OwensQ(2, 2.92, 4.2135, 0, 2.0407)
OwensQOwen(2, 2.92, 4.2135, 0, 2.0407)
```

OwensT   *Owen's T-function*

Description

Calculates the definite integral from 0 to a of
exp(-0.5*h^2*(1+x^2))/(1+x^2)/(2*pi).

Usage

```
OwensT(h, a)
```

Arguments

h	parameter h
a	upper limit of integration

Details

The function is an R port of FORTRAN code given in the references and MATLAB code given by John Burkardt under the GNU LGPL license.

The arguments of OwensT() have to be scalars because the implementation doesn't vectorize.

Value

Numerical value of the definite integral.

Note

This function is only needed as auxiliary in OwensQOwen.
But may be useful for others.

Author(s)

MATLAB code by J. Burkardt, R port by D. Labes

References

Goedhart PW, Jansen MJW. *Remark AS R89: A Remark on Algorithm AS 76: An Integral Useful in Calculating Central t and Bivariate Normal Probabilities.* J Royal Stat Soc C. 1992;41(2):496–7. doi:10.2307/2347586

Boys R. *Algorithm AS R80: A Remark on Algorithm AS 76: An Integral Useful in Calculating Non-central t and Bivariate Normal Probabilities.* J Royal Stat Soc C. 1989;38(3):580–2. doi:10.2307/2347755

Thomas GE. *Remark ASR 65: A Remark on Algorithm AS76: An Integral Useful in Calculating Non-Central t and Bivariate Normal Probabilities.* J Royal Stat Soc C. 1986;35(3):310–2. doi:10.2307/2348031

Chou Y-M. *Remark AS R55: A Remark on Algorithm AS 76: An Integral Useful in Calculating Non-central T and Bivariate Normal Probabilities.* J Royal Stat Soc C. 1985;34(1):100–1. doi:10.2307/2347894

Thomas GE. *Remark AS R30: A Remark on Algorithm AS 76: An Integral Useful in Calculating Non-Central t and Bivariate Normal Probabilities.* J Royal Stat Soc C. 1979;28(1):113. doi:10.2307/2346833

Young JC, Minder C. *Algorithm AS 76: An Integral Useful in Calculating Non-Central t and Bivariate Normal Probabilities.* J Royal Stat Soc C. 1974;23(3):455–7. doi:10.2307/2347148

Burkardt J. *ASA076. Owen's T Function.* https://people.math.sc.edu/Burkardt/f_src/asa076/asa076.html

Owen DB. *Tables for Computing Bivariate Normal Probabilities.* Ann Math Stat. 1956;27(4):1075–90. doi:10.1214/aoms/1177728074

See Also

OwensQOwen, OwensQ

Examples

```
OwensT(2.5, 0.75)
# should give [1]  0.002986697
# value from Owen's tables is 0.002987
OwensT(2.5, -0.75)
# should give [1] -0.002986697
```

---

pa.ABE   *Power analysis for average bioequivalence (ABE)*

Description

An analysis tool for exploration/visualization of the impact of expected values (CV, theta0, reduced sample size due to drop-outs) on power of BE decision via ABE if these values deviate from the ones assumed in planning the sample size of the study.

Usage

```
pa.ABE(CV, theta0 = 0.95, targetpower = 0.8, minpower = 0.7, design = "2x2", ...)
## S3 method for class 'pwrA'
print(x, digits = 4, plotit = TRUE, ...)
## S3 method for class 'pwrA'
plot(x, pct = TRUE, ratiolabel = "theta0", cols = c("blue", "red"), ...)
```

Arguments

CV
: Coefficient of variation as ratio (not percent).
: In case of cross-over studies this is the within-subject CV.

theta0
: 'True' or assumed T/R ratio. Often named GMR.
: Must be given as ratio.

targetpower
: Power to achieve at least in sample size estimation. Must be >0 and <1.
: Typical values are 0.8 or 0.9. Defaults to 0.8.
: Note that targetpower < 0.5 doesn't make much sense.

minpower
: Minimum acceptable power to have if deviating from assumptions for sample size plan.
: Has to be lower than targetpower. Defaults to 0.7.
: minpower < 0.5 doesn't make much sense.

design
: Character string describing the study design.
: See known.designs() for designs covered in this package.

...
: More arguments to pass to power.TOST().
: F.i. alpha, theta1, theta2 or robust if other values then the defaults for these arguments are needed.
: See man page of power.TOST().

More arguments passed to the S3 methods. Here currently ignored.

Additional arguments of the S3 methods:

x	Object of class `'pwrA'`.
digits	Digits for rounding power in printing. The '…' argument is currently ignored in `print()`.
plotit	If set to `TRUE`, the default, the print method calls `plot(x)` if R is running interactively.
pct	If set to `TRUE` (the default) scales CV, theta0, and power in percent in `plot()`. Else they will be given as ratios, the usual standard in PowerTOST.
ratiolabel	Label of the T/R-ratio. Can be set to any string, e.g. to `"GMR"`. Defaults to `"theta0"`, the usual standard in PowerTOST.
cols	Colors for the plots. `cols[1]` gives the color for plotting points with `power>targetpower`. From `targetpower` toward `minpower` the color changes gradually to `cols[2]`.

Details

Power calculations are done via `power.TOST()` and calculations of CV and theta0 which gave a power=minpower are derived via R base [uniroot](#). While one of the parameters (CV, theta0, n) is varied, the respective two others are kept constant. The tool shows the relative impact of single parameters on power.
The tool takes a minimum of 12 subjects as required in most BE guidances into account.

It should be kept in mind that this is **not** a substitute for the 'Sensitivity Analysis' recommended in ICH-E9. In a real study a combination of all effects occurs simultaneously. It is up to *you* to decide on reasonable combinations and analyze their respective power.

Value

Returns a list with class `"pwrA"` with the components

plan	A data.frame with the result of the sample size estimation. See output of `sampleN.TOST()`.
paCV	A data.frame with value pairs CV, pwr for impact of deviations from CV.
paGMR	A data.frame with value pairs theta0, pwr for impact of deviations from theta0 (GMR).
paN	A data.frame with value pairs N, pwr for impact of deviations from planned N (dropouts).
method	Method of BE decision. Here "ABE".
minpower	Minimum acceptable power.

The class `'pwrA'` has the S3 methods `print()` and `plot()`. See [pa.scABE](#) for usage.

Note

The code of deviations from planned sample size tries to keep the degree of imbalance as low as possible between (sequence) groups. This results in a lesser decrease of power than more extreme dropout-patterns.

Author(s)

Idea and original code by H. Schütz with modifications by D. Labes to use PowerTOST infrastructure.

References

Schütz H. *Deviating from assumptions.* August 08, 2014. BEBA Forum

See Also

power.TOST, known.designs, pa.scABE, pa.NTIDFDA

Examples

```
# using the defaults
# design="2x2", targetpower=0.8, minpower=0.7, theta0/GMR=0.95
# BE margins from defaults of sampleN.TOST() 0.8 ... 1.25
# print & plot implicitly
pa.ABE(CV = 0.2)
# print & plot

res <- pa.ABE(CV = 0.2)
print(res, plotit = FALSE)            # print only
plot(res, pct = FALSE, ratiolabel = "GMR") # changed from defaults
```

---

pa.NTID   *Power analysis for scaled ABE for NTIDs*

Description

An analysis tool for exploration/visualization of the impact of expected values (CV, theta0, reduced sample size due to drop-outs) on power of BE decision via scABE for narrow therapeutic drugs (NTIDs) if these values deviate from the ones assumed in planning the sample size of the study.
The only implemented design is the full replicate design "2x2x4" according to the FDA's warfarin guidance.

Usage

```
pa.NTID(CV, theta0 = 0.975, targetpower = 0.8, minpower = 0.7, ...)
```

Arguments

CV	Coefficient of variation of the intra-subject variabilities of Test and Reference as ratio (not percent).
	Here only the case CVwT == CVwR is implemented, *i.e.*, CV has to be a scalar (length(CV) == 1).
theta0	'True' or assumed T/R ratio. Often named GMR.
	Must be given as ratio. Defaults here to 0.975.

targetpower	Power to achieve at least in sample size estimation. Must be >0 and <1. Typical values are 0.8 or 0.9. Defaults to 0.8. Note that targetpower < 0.5 doesn't make much sense.
minpower	Minimum acceptable power to have if deviating from assumptions for sample size plan. Has to be lower than targetpower. Defaults to 0.7. minpower < 0.5 doesn't make much sense.
...	More arguments to pass to power.NTID(). F.i., alpha, theta1, theta2 or nsims if other values than the defaults for these arguments are needed. See man page of power.NTID().

Details

Power calculations are done via power.NTID() and calculations of CV and theta0 which result in minpower are obtained via uniroot().
While one of the parameters (CV, theta0, n) is varied, the respective two others are kept constant. The tool shows the relative impact of single parameters on power.
The tool takes a minimum of 12 subjects into account as demanded in most BE guidances. However, it should be kept in mind that the FDA requires at least 24 subjects to be enrolled in studies intended for reference-scaling.

It should be kept in mind that this is **not** a substitute for the 'Sensitivity Analysis' recommended in ICH-E9. In a real study a combination of all effects occurs simultaneously. It is up to *you* to decide on reasonable combinations and analyze their respective power.

Value

Returns a list with class 'pwrA' with the components

plan	A data.frame with the result of the sample size estimation. See output of sampleN.NTID().
paCV	A data.frame with value pairs CV, pwr for impact of deviations from CV.
paGMR	A data.frame with value pairs theta0, pwr for impact of deviations from theta0 (GMR).
paN	A data.frame with value pairs N, pwr for impact of deviations from planned N (dropouts).
method	Method of BE decision. Here "NTID".
regulator	Here "FDA".
minpower	Minimum acceptable power from the call of the function.

The class 'pwrA' has the S3 methods print() and plot(). See [pa.ABE](#) for usage.

Warning

Be extremly carefull if your sample size plan has extremely small CV near or below 0.05 (5%). Adapt in that case your expected true ratio (theta0) to values nearer to 1 to not run into errors and/or long execution times.

Note

The code for impact of deviations from planned sample size tries to keep the degree of imbalance as low as possible between (sequence) groups. This results in a lesser decrease of power than more extreme dropout-patterns.

Author(s)

D. Labes according to code by H. Schütz for `pa.ABE()` and `pa.scABE()`.

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Warfarin Sodium.* Recommended Dec 2012. download

Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Draft Guidance for Industry. Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.* August 2021. download

Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, Muldowney L, Chen ML, Davit B, Conner D, Woodcock J. *Novel bioequivalence approach for narrow therapeutic index drugs.* Clin Pharmacol Ther. 2015;97(3):286–91. doi:10.1002/cpt.28

Jiang W, Makhlouf F, Schuirmann DJ, Zhang X, Zheng N, Conner D, Yu LX, Lionberger R. *A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion.* AAPS J. 2015;17(4):891–901. doi:10.1208/s1224801597535

Endrényi L, Tóthfalusi L. *Determination of Bioequivalence for Drugs with Narrow Therapeutic Index: Reduction of the Regulatory Burden.* J Pharm Pharm Sci. 2013;16(5):676–82. open access

See Also

`power.NTID`, `print.pwrA`, `plot.pwrA`, `pa.ABE`, `pa.scABE`

Examples

```
# using the defaults:
# targetpower=0.8, minpower=0.7, theta0/GMR=0.975
# BE margins from defaults of sampleN.NTID() 0.9002 ... 1.1108
# 1E5 sims in power.NTID()
# not run due to timing policy of CRAN for examples
# may run some ten seconds or more

plot(pa.NTID(CV=0.1))
```

---

pa.scABE   *Power analysis for scaled average bioequivalence (scABE)*

Description

An analysis tool for exploration/visualization of the impact of expected values (CV, theta0, reduced sample size due to drop-outs) on power of BE decision via scABE (for highly variable drugs) if these values deviate from the ones assumed in planning the sample size of the study.

Usage

```
pa.scABE(CV, theta0 = 0.9, targetpower = 0.8, minpower = 0.7,
        design = c("2x3x3", "2x2x4", "2x2x3"),
        regulator = c("EMA", "HC", "FDA", "GCC"), ...)
```

Arguments

CV	Coefficient of variation of the intra-subject variability as ratio (not percent). Here only the case CVwT=CVwR is implemented, *i.e.*, CV has to be a scalar.
theta0	'True' or assumed T/R ratio. Often named GMR. Must be given as ratio. Defaults to 0.9 here since HVD have a greater scatter in point estimates of T/R.
targetpower	Power to achieve at least in sample size estimation. Must be >0 and <1. Typical values are 0.8 or 0.9. Defaults to 0.8. Note that targetpower < 0.5 doesn't make much sense.
minpower	Minimum acceptable power to have if deviating from assumptions for sample size plan. Has to lower than targetpower. Defaults to 0.7. minpower < 0.5 doesn't make much sense.
design	Character string describing the study design. Defaults to 2x3x3, the partial replicate design (TRR|RTR|RRT).
regulator	Character string describing the scaled ABE method recommended by the regulatory bodies "EMA", "HC", "FDA" or "GCC". Defaults to "EMA", method of scaled (expanded) bioequivalence limits.
...	More arguments to pass to power.scABEL() or power.RSABE(). F.i., alpha, theta1, theta2 or nsims if other values than the defaults for these arguments are needed. See man pages of power.scABEL() or power.RSABE().

Details

Power calculations are done via power.scABEL() or power.RSABE() and calculations of CV and theta0 which result in minpower derived via R base uniroot.
While one of the parameters (CV, GMR, N) is varied, the respective two others are kept constant. The tool shows the relative impact of single parameters on power.

The tool takes a minimum of 12 subjects as required in most BE guidances into account. However, the sample size will be increased from the estimated one if one of the following conditions is applicable:

- The FDA requires at least 24 subjects *enrolled* in studies intended for reference-scaling.
- The EMA requires at least 12 *eligible* subjects in the sequence RTR of the TRT|RTR-design (hence the minimum sample size is 24).

You should be aware that this is **not** a substitute for the "Sensitivity Analysis" recommended in ICH-E9. In a real study a combination of all effects occurs simultaneously. It is up to *you* to decide on reasonable combinations and analyze their respective power.

Value

Returns a list with class `'pwrA'` with the components

plan	A data.frame with the result of the sample size estimation. See output of `sampleN.scABEL()` or `sampleN.RSABE()`.
paCV	A data.frame with value pairs CV, pwr for impact of deviations from CV.
paGMR	A data.frame with value pairs theta0, pwr for impact of deviations from theta0 (GMR).
paN	A data.frame with value pairs N, pwr for impact of deviations from planned N (dropouts).
method	Method of BE decision. Here fix = "scABE".
regulator	"EMA", "HC", or "FDA".
minpower	Minimum acceptable power from the call of the function.

The class `'pwrA'` has the S3 methods `print()` and `plot()`. See [pa.ABE](#) for usage.

Note

The code for impact of deviations from planned sample size tries to keep the degree of imbalance as low as possible between (sequence) groups. This results in a lesser decrease of power than more extreme dropout-patterns.

Author(s)

Idea and original code by H. Schütz with modifications by D. Labes to use PowerTOST infrastructure.

References

Schütz H. *Deviating from assumptions.* August 08, 2014. [BEBA Forum](#)

See Also

[power.scABEL](#), [power.RSABE](#), [known.designs](#), [print.pwrA](#), [plot.pwrA](#), [pa.ABE](#), [pa.NTIDFDA](#)

Examples

```
# Implicitely using the defaults:
# design = "2x3x3", targetpower = 0.8, minpower = 0.7,
# theta0 = 0.9, GMR = 0.90, regulator = "EMA"
# widened BE margins from defaults of sampleN.scABEL() 0.7462 ... 1.3402
# 1E5 sims in power.scABEL()
# not run due to timing policy of CRAN, may run some ten seconds

# Implicit print & plot
pa.scABE(CV = 0.4)
```

---

power.2TOST   *Power for two simultaneous TOST procedures*

Description

Calculates the exact power of two simultaneous TOST procedures (where the two parameters of the two TOSTs are correlated with some correlation) for various study designs used in BE studies

Usage

```
power.2TOST(alpha = c(0.05, 0.05), logscale = TRUE, theta0, theta1, theta2,
            CV, n, rho, design = "2x2", robust = FALSE, nsims, setseed = TRUE,
            details = FALSE)
```

Arguments

alpha
: Vector; contains one-sided significance level for each of the two TOSTs.
  For one TOST, by convention mostly set to 0.05.

logscale
: Should the data used on log-transformed (TRUE, default) or on original scale (FALSE)?

theta1
: Vector; contains lower bioequivalence limit for each of the two TOSTs.
  In case of logscale=TRUE it is given as ratio, otherwise as diff. to 1.
  Defaults to c(0.8, 0.8) if logscale=TRUE or to c(-0.2, -0.2) if logscale=FALSE.

theta2
: Vector; contains upper bioequivalence limit for each of the two TOSTS.
  If not given theta2 will be calculated as 1/theta1 if logscale=TRUE
  or as -theta1 if logscale=FALSE.

theta0
: Vector; contains 'true' assumed bioequivalence ratio for each of the two TOSTs.
  In case of logscale=TRUE each element must be given as ratio,
  otherwise as difference to 1. See examples.
  Defaults to c(0.95, 0.95) if logscale=TRUE or to c(0.05, 0.05) if logscale=FALSE.

CV
: Vector of coefficient of variations (given as as ratio, *e.g.*, 0.2 for 20%).
  In case of cross-over studies this is the within-subject CV,
  in case of a parallel-group design the CV of the total variability.
  In case of logscale=FALSE CV is assumed to be the respective standard deviation.

n	Number of subjects under study. Is total number if given as scalar, else number of subjects in the (sequence) groups. In the latter case the length of n vector has to be equal to the number of (sequence) groups.
rho	Correlation between the two PK metrics (*e.g.*, AUC and Cmax) under consideration. This is defined as correlation between the estimator of the treatment difference of PK metric one and the estimator of the treatment difference of PK metric two. Has to be within $\{-1, +1\}$.
design	Character string describing the study design. See known.designs() for designs covered in this package.
robust	Defaults to FALSE. With that value the usual degrees of freedom will be used. Setting to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as n-seq. See known.designs()$df2 for designs covered in this package. Has only effect for higher-order crossover designs.
nsims	Number of studies to simulate. Defaults to 1E5.
setseed	Logical; if TRUE, the default, a seed of 1234567 is set.
details	Logical; if TRUE, run time will be printed. Defaults to FALSE.

Details

Calculations are based on simulations and follow the distributional properties as described in Phillips. This is in contrast to the calculations via the 4-dimensional non-central *t*-distribution as described in Hua *et al.* which was implemented in versions up to 1.4-6.

The formulas cover balanced and unbalanced studies w.r.t (sequence) groups.

In case of parallel group design and higher order crossover designs (replicate crossover or crossover with more than two treatments) the calculations are based on the assumption of equal variances for Test and Reference products under consideration.

The formulas for the paired means 'design' do not take an additional correlation parameter into account. They are solely based on the paired *t*-test (TOST of differences = zero).

Value

Value of power.

Note

If n is given as scalar (total sample size) and this number is not divisible by the number of (sequence) groups of the design an unbalanced design with small imbalance is assumed. A corresponding message is thrown showing the assumed numbers of subjects in (sequence) groups.
The function does not vectorize properly if design is a vector. Moreover, theta0 and CV must be of length two, thus further vectorizing is not possible.
Other vector input is not tested yet.

Author(s)

B. Lang, D. Labes

References

Phillips KF. *Power for Testing Multiple Instances of the Two One-Sided Tests Procedure.* Int J Biostat. 2009;5(1):Article 15.

Hua SY, Xu S, D'Agostino RB Sr. *Multiplicity adjustments in testing for bioequivalence.* Stat Med. 2015;34(2):215–31. doi:10.1002/sim.6247

Lang B, Fleischer F. *Letter to the Editor: Comments on 'Multiplicity adjustments in testing for bioequivalence.'* Stat Med. 2016;35(14):2479–80. doi:10.1002/sim.6488

See Also

sampleN.2TOST, known.designs

Examples

```
# Power for the 2x2x2 cross-over design with 24 subjects, intra-subject
# standard deviation of 0.3 (CV = 30.7%) and assumed ratios of 1.05 for both
# parameters, and correlation 0.75 between parameters (using all the other
# default values)
power.2TOST(theta0 = rep(1.05, 2), CV = rep(se2CV(0.3), 2),
            n = 24, rho = 0.75)
# should give: 0.38849

# Setting as before but use rho 1 and high number of simulations
# to reproduce result of power.TOST()
p1 <- power.2TOST(theta0 = rep(1.05, 2), CV = rep(se2CV(0.3), 2),
                  n = 24, rho = 1, nsims=1E7)
p2 <- power.TOST(theta0 = 1.05, CV = se2CV(0.3), n = 24)
all.equal(p1, p2, tolerance = 1e-04)
```

---

power.dp	*Power of dose-proportionality studies evaluated via Power model*

Description

Calculates the power of dose-proportionality studies using the power model for crossover (Latin square) or parallel group designs via a confidence interval equivalence criterion.

Usage

```
power.dp(alpha = 0.05, CV, doses, n, beta0, theta1 = 0.8, theta2 = 1/theta1,
        design = c("crossover", "parallel", "IBD"), dm = NULL, CVb)
```

Arguments

alpha	Type 1 error. Commonly set to 0.05.
CV	Coefficient of variation for intra-subject variability if design="crossover" or CV of total variability in case of design="parallel".
doses	Vector of dose levels. At least two doses have to be given.
n	Number of subjects. Is total number if given as scalar, else number of subjects in the (sequence) groups. In the latter case the length of n vector has to be the same as length of vector doses. n has to be >2.
beta0	'True' slope of power model. If missing defaults to 1+log(0.95)/log(rd) where rd is the ratio of highest to lowest dose.
theta1	Lower acceptance limit for the ratio of dose normalized means (Rdmn). Transformes into slope acceptance range as described under item beta0.
theta2	Upper acceptance limit for the ratio of dose normalized means (Rdmn).
design	Crossover design (default), parallel group design or incomplete block design (IBD). Crossover design means Latin square design with number of doses as dimension.
dm	'Design matrix' of the incomplete block design (IBD) if design="IBD". This matrix contains the sequences in rows and periods in columns. The entry (i, j) of the design matrix corresponds to the dose (index) a subject with i-th sequence gets in the j-th period. Can be obtained f.i. via functions of package crossdes or via function bib.CL().
CVb	Coefficient of variation of the between-subject variability. Only necessary if design="IBD". Will be set to 2*CV if missing. This is only a crude rule of thumb. Better obtain an estimate of CVb from a previous crossover study. Set CVb=0 if an all-effects-fixed model shall be used. This model gives higher power than the random subject effects model.

Details

The power calculations are based on TOST for testing equivalence of the slope of the power model with alternativ hypothesis slope = 1.
Power is calculated via non-central t-approximation only.
The calculations are based on mixed effects model (random intercept aka random subject effect).
For design="cossover" or design="parallel" the results coincide with all-effects-fixed model.

Value

Value of power according to the input arguments.

Warning

This function is 'experimental' only since it is not thoroughly tested yet. Especially for design="IBD" reliable test cases are missing.

Author(s)

D. Labes

References

Patterson S, Jones B. *Bioequivalence and Statistics in Clinical Pharmacology.* Boca Raton: Chapman & Hall/CRC: 2006. p. 239.
(contains presumably a bug)

Sethuraman VS, Leonov S, Squassante L, Mitchell TR, Hale MD. *Sample size calculation for the Power Model for dose proportionality studies.* Pharm Stat. 2007;6(1):35–41. doi:10.1002/pst.241

Hummel J, McKendrick S, Brindley C, French R. *Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion.* Pharm. Stat. 2009;8(1):38–49. doi:10.1002/pst.326

See Also

sampleN.dp, bib.CL

Examples

```
# using all the defaults, i.e. latin square crossover design, alpha=0.05,
# beta0=1+log(0.95)/log(rd), theta1=0.8, theta2=1.25
power.dp(CV = 0.2, doses = c(1,2,8), n = 15)
#
# period balanced IBD with 3 doses, 2 periods and 3 sequences,
ibd <- matrix(c(1, 2, 3, 2, 3, 1), nrow = 3, ncol = 2)
power.dp(CV = 0.2, doses = c(1,2,8), n = 12, design = "IBD", dm = ibd)
# considerably lower than 3x3 Latin square
```

---

power.HVNTID   *(Empirical) Power for BE decision via FDA method for highly variable NTIDs*

Description

This function performs the power calculation of the BE decision via the FDA's method for highly variable narrow therapeutic index drugs (NTIDs) as described in respective guidances based on simulations. The study design could be the full replicate design 2x2x4 with 4-periods (TRTR|RTRT) or the 2x2x3 replicate design with 3-periods and sequences TRT|RTR.

Usage

```
power.HVNTID(alpha = 0.05, theta1, theta2, theta0, CV, n, design = c("2x2x4", "2x2x3"),
             nsims = 1e+05, details = FALSE, setseed = TRUE)
```

Arguments

alpha	Type I error probability, significance level. Commonly set to 0.05.
theta1	Conventional lower ABE limit to be applied in the FDA procedure. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the FDA procedure. Defaults to 1.25 if not given explicitly.
theta0	'True' or assumed T/R ratio. Defaults to 0.95 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). • If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR). • If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
n	Number of subjects under study. May be given as vector. In that case it is assumed that n contains the number of subjects per sequence groups. Attention! In case of the "2x2x3" (TRT|RTR) design the order of sample sizes is important if given as vector. n[1] is for sequence group 'TRT' and n[2] is for sequence group 'RTR'. If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown showing the numbers of subjects in the sequence groups.
design	Design of the study to be planned. "2x2x4" is the full replicate design with 2 sequences and 4 periods (TRTR|RTRT). "2x2x3" is the 3-period ful replicate design with sequences TRT|RTR. Defaults to design="2x2x4".
nsims	Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+5.
details	If set to TRUE the computational time is shown as well as the components for the BE decision. p(BE-ABE) is the simulated probability for the conventional ABE test. p(BE-sratio) is the probability that the upper 90% confidence limit of the ratio of sWT/sWR is < 2.5.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(123456) is issued if setseed=TRUE, the default.

Details

For deciding BE the study must pass the conventional ABE test (90% CI within the acceptance range) and additional the test that the ratio of sWT/sWR is < 2.5.

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on this method.
Details can be found in a document `Implementation_scaledABE_sims` located in the /doc subdirectory of the package.

Value

Returns the value of the (empirical) power if argument `details=FALSE`.
Returns a named vector if argument `details=TRUE`.
p(BE) is the power, p(BE-ABE) is the power of the ABE test alone and p(BE-sratio) is the power of the criterion 'ratio of sWT/sWR is <= 2.5' alone.

Note

The FD's guidances recommend only the full replicate design "2x2x4" (TRTR|RTRT). The results for the design "2x2x3" (TRT|RTR) are to be considered as experimental since at present not thorougly tested.

The method is also required by China's Center of Drug Evaluation.

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Dabigatran Etexilate Mesylate.* Recommended Jun 2012; Revised Sep 2015, Jul 2017. download

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Rivaroxaban.* Recommended Sep 2015. download

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Edoxaban Tosylate.* Recommended May 2017; Revised Mar 2020. download

See Also

sampleN.HVNTID and power.NTIDFDA, sampleN.NTIDFDA for NTIDs with low variability

Examples

```
# using the defaults:
# GMR=0.95, theta1=0.8, theta2=1.25, full replicate design 2x2x4, 100,000 simulations
# and a CV of 0.3 (=30%) for both Reference and Test, with 24 subjects, balanced
power.HVNTID(CV = 0.3, n = 24)
# should give a power of 0.86354
```

---

power.noninf   *Power of the one-sided non-inferiority t-test*

Description

Function calculates of the power of the one-sided non-inferiority *t*-test for normal or log-normal distributed data.

Usage

```
power.noninf(alpha = 0.025, logscale = TRUE, margin, theta0, CV, n,
             design = "2x2", robust = FALSE)
```

Arguments

alpha	Significance level (one-sided). Defaults here to 0.025.
logscale	Should the data used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	'True' or assumed T/R ratio or difference. In case of logscale=TRUE it must be given as ratio T/R. If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of margin and CV need also be given relative to the reference mean (specified as ratio). Defaults to 0.95 if logscale=TRUE or to -0.05 if logscale=FALSE
margin	Non-inferiority margin. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV and theta0 need also be given relative to the reference mean (specified as ratio). Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
CV	In case of logscale=TRUE the (geometric) coefficient of variation given as ratio. If logscale=FALSE the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of theta0, theta1 and theta2 need also be given relative to the reference mean (specified as ratio). In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.
n	Number of subjects under study. Is total number if given as scalar, else number of subjects in the (sequence)

groups. In the latter case the length of the n vector has to be equal to the number of (sequence) groups.

design
:   Character string describing the study design.
    See known.designs for designs covered in this package.

robust
:   Defaults to FALSE. With that value the usual degrees of freedom will be used.
    Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as n-seq.
    See known.designs()$df2 for designs covered in this package.
    Has only effect for higher-order crossover designs.

Details

The power is calculated exact via non-central *t*-distribution.

Notes on the underlying hypotheses

If the supplied margin is < 0 (logscale=FALSE) or < 1 (logscale=TRUE), then it is assumed higher response values are better. The hypotheses are

H0: theta0 <= margin vs. H1: theta0 > margin

where theta0 = mean(test)-mean(reference) if logscale=FALSE

or

H0: log(theta0) <= log(margin) vs. H1: log(theta0) > log(margin)

where theta0 = mean(test)/mean(reference) if logscale=TRUE.

If the supplied margin is > 0 (logscale=FALSE) or > 1 (logscale=TRUE), then it is assumed lower response values are better. The hypotheses are

H0: theta0 >= margin vs. H1: theta0 < margin

where theta0 = mean(test)-mean(reference) if logscale=FALSE

or

H0: log(theta0) >= log(margin) vs. H1: log(theta0) < log(margin)

where theta0 = mean(test)/mean(reference) if logscale=TRUE.

This latter case may also be considered as 'non-superiority'.

Value

Value of power according to the input arguments.

Warning

The function does not vectorize if design is a vector.
The function vectorize properly if CV or theta0 are vectors.
Other vector input is not tested yet.

Note

This function does not rely on TOST but may be useful in planning BE studies if the question is not equivalence but 'non-superiority'.
Hint: Evaluation of Fluctuation in the EMEA's Note for Guidance between a modified release formulation and an immediate release product.

Author(s)

D. Labes

References

Julious SA. *Sample sizes for clinical trials with Normal data.* Stat Med. 2004;23(12):1921–86.
doi:10.1002/sim.1783

See Also

known.designs, sampleN.noninf

Examples

```
# using all the defaults: margin=0.8, theta0=0.95, alpha=0.025
# log-transformed, design="2x2"
# should give: 0.4916748
power.noninf(CV=0.3, n=24)
```

---

power.NTID   *(Empirical) Power for BE decision via FDA method for NTIDs*

Description

This function performs the power calculation of the BE decision via the FDA's method for narrow
therapeutic index drugs (NTIDs) by simulations. The study design could be the full replicate design
2x2x4 with 4-periods (TRTR|RTRT) or the 2x2x3 replicate design with sequences TRT|RTR.

Usage

```
power.NTID(alpha = 0.05, theta1, theta2, theta0, CV, n, design=c("2x2x4", "2x2x3"),
           nsims = 1e+05, details = FALSE, setseed = TRUE)
```

Arguments

alpha	Type I error probability, significance level. Conventionally mostly set to 0.05.
theta1	Conventional lower ABE limit to be applied in the FDA procedure. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the FDA procedure. Defaults to 1.25 if not given explicitly.
theta0	'True' or assumed T/R ratio. Attention! Defaults here to 0.975 if not given explicitly. The value was chosen closer to 1 because the potency (contents) settings for NTIDs are tightened by the FDA.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).

- If given as a scalar (`length(CV) == 1`) the *same* CV of Test and Reference is assumed (homoscedasticity, `CVwT == CVwR`).
- If given as a vector (`length(CV) == 2`), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in `CV[1]` and the one of the Reference in the `CV[2]`.

n	Number of subjects under study.
	May be given as vector. In that case it is assumed that n contains the number of subjects per sequence groups.
	Attention! In case of the "2x2x3" (TRT|RTR) design the order of sample sizes important if given as vector. `n[1]` is for sequence group 'TRT' and `n[2]` is for sequence group 'RTR'.
	If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown showing the numbers of subjects in the sequence groups.
design	Design of the study to be planned.
	"2x2x4" is the full replicate design with 2 sequences and 4 periods (TRTR|RTRT).
	"2x2x3" is the full replicate design with 2 sequences and 3 periods (TRT|RTR).
	Defaults to `design="2x2x4"`.
nsims	Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+5.
details	If set to TRUE the computational time is shown as well as the components for the BE decision.
	`p(BE-ABE)` is the simulated probability for the conventional ABE test.
	`p(BE-sABEc)` is the probability that the 95% CI of the scaled ABE criterion is ≤ 0.
	`p(BE-sratio)` is the probability that the upper confidence limit of $\sigma_{wT}/\sigma_{wR} \leq 2.5$.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a `set.seed(123456)` is issued if `setseed = TRUE`, the default.

Details

The linearized scaled ABE criterion is calculated according to the SAS code given in the FDA's guidances. For deciding BE the study must pass that criterion, the conventional ABE test, and that the upper confidence limit of $\sigma_{wT}/\sigma_{wR} \leq 2.5$.

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on these method.
Details can be found in a document `Implementation_scaledABE_sims` located in the /doc subdirectory of the package.

Value

Returns the value of the (empirical) power if argument `details = FALSE`.
Returns a named vector if argument `details = TRUE`, where `p(BE)` is the (overall) power, `p(BE-sABEc)`

is the power of the BE test via scaled ABE criterion alone, p(BE-ABE) is the power of the conventional ABE test alone, and p(BE-sratio) is the power of the criterion 'upper confidence limit of $\sigma_{wT}/\sigma_{wR} \leq 2.5$' alone.

Note

The FDA's method is described for the ABE limits 0.8 ... 1.25 only. Setting theta1, theta2 to other values may not be reasonable and is not tested.
The results for the design "2x2x3" are to be considered as experimental since at present not thorougly tested.

The method is also required by China's Center of Drug Evaluation.

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Warfarin Sodium.* Recommended Dec 2012. download

Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Draft Guidance for Industry. Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.* August 2021. download

Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, Muldowney L, Chen ML, Davit B, Conner D, Woodcock J. *Novel bioequivalence approach for narrow therapeutic index drugs.* Clin Pharmacol Ther. 2015;97(3):286–91. doi:10.1002/cpt.28

Jiang W, Makhlouf F, Schuirmann DJ, Zhang X, Zheng N, Conner D, Yu LX, Lionberger R. *A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion.* AAPS J. 2015;17(4):891–901. doi:10.1208/s1224801597535

Endrényi L, Tóthfalusi L. *Determination of Bioequivalence for Drugs with Narrow Therapeutic Index: Reduction of the Regulatory Burden.* J Pharm Pharm Sci. 2013;16(5):676–82. open access

See Also

sampleN.NTID
and power.HVNTID, sampleN.HVNTID for NTIDs with high variability

Examples

```
# using the all defaults:
# GMR=0.975, theta1=0.8, theta2=1.25, 100,000 simulations
# and a CV of 0.1 (= 10%) with 12 subjects, balanced
power.NTID(CV = 0.1, n = 12)
# should give a power of 0.62553
```

---

power.RatioF	*Power for equivalence of the ratio of two means with normality on original scale*

Description

Calculates the power of the test of equivalence of the ratio of two means with normality on original scale.

This test is based on Fieller's confidence ('fiducial') interval and Sasabuchi's test (a TOST procedure as well).

Usage

```
power.RatioF(alpha = 0.025, theta1 = 0.8, theta2, theta0 = 0.95,
             CV, CVb, n, design = "2x2", setseed=TRUE)
```

Arguments

alpha	Type I error probability, aka significance level. Defaults here to 0.025 because this function is intended for studies with clinical endpoints.
theta1	Lower bioequivalence limit. Typically 0.8 (default).
theta2	Upper bioequivalence limit. Typically 1.25. Is set to 1/theta1 if missing.
theta0	'True' or assumed T/R ratio. Typically set to 0.95 for planning.
CV	Coefficient of variation as ratio. In case of design="parallel" this is the CV of the total variability, in case of design="2x2" the intra-subject CV (CVw in the reference).
CVb	CV of the between-subject variability. Only necessary for design="2x2".
n	Number of subjects to be planned. n is for both designs implemented the **total** number of subjects.
design	A character string describing the study design. design="parallel" or design="2x2" allowed for a two-parallel group design or a classical TR|RT crossover design.
setseed	If set to TRUE the dependence of the power from the state of the random number generator is avoided. With setseed = FALSE you may see the dependence from the state of the random number generator.

Details

The power is calculated exact using the bivariate non-central *t*-distribution via function [pmvt](#) of the package mvtnorm.

Due to the calculation method of the used package mvtnorm – randomized Quasi-Monte-Carlo – these probabilities are dependent from the state of the random number generator within the precision of the power. See argument setseed.

Value

Value of power according to the input.

Note

This function is intended for studies with clinical endpoints where the 95% confidence intervals are usually used for equivalence testing.
Therefore, alpha defaults here to 0.025 (see EMEA 2000).

The formulas given in the references rely on the assumption of equal variances in the two treatment groups for the parallel group design or on assuming equal within-subject and between-subject variabilities for the 2×2 crossover design.

Author(s)

D. Labes

References

Fieller EC. *Some Problems in Interval Estimation.* J Royal Stat Soc B. 1954;16(2):175–85. doi:10.1111/j.25176161.1954.tb00159.x

Sasabuchi S. *A test of a multivariate normal mean with composite hypotheses determined by linear inequalities.* Biometrika. 1980;67(2):429–39. doi:10.1093/biomet/67.2.429

Hauschke D, Kieser M, Diletti E, Burke M. *Sample size determination for proving equivalence based on the ratio of two means for normally distributed data.* Stat Med. 1999;18(1):93–105.

Hauschke D, Steinijans V, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: Wiley; 2007. Chapter 10.

European Agency for the Evaluation of Medicinal Products, CPMP. *Points to Consider on Switching between Superiority and Non-Inferiority.* London, 27 July 2000. CPMP/EWP/482/99

See Also

sampleN.RatioF

Examples

```
# power for alpha=0.025, ratio0=0.95, theta1=0.8, theta2=1/theta1=1.25
# within-subject CV=0.2, between-subject CV=0.4
# 2x2 crossover study, n=24
# using all the defaults:
power.RatioF(CV = 0.2, CVb = 0.4, n = 24)
# gives [1] 0.7315357
```

power.RSABE   *(Empirical) Power for BE decision via linearized scaled ABE criterion*

Description

This function performs the power calculation of the BE decision via linearized scaled ABE criterion by simulations as recommended by the FDA.

Usage

```
power.RSABE(alpha = 0.05, theta1, theta2, theta0, CV, n,
            design = c("2x3x3", "2x2x4", "2x2x3"), regulator,
            nsims = 1e+05, details = FALSE, setseed=TRUE)
```

Arguments

alpha	Type I error probability, significance level. Conventionally mostly set to 0.05.
theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). - If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR). - If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
n	Number of subjects under study. May be given as vector. In that case it is assumed that n contains the number of subjects in the sequence groups. If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown showing the numbers of subjects in sequence groups used. Attention! In case of the "2x2x3" (TRT|RTR) design the order of sample sizes / sequence is important if given as a vector. n[1] is for sequence group 'TRT' and n[2] is for sequence group 'RTR'.
design	Design of the study. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods.

"2x2x3" is a full replicate design with 2 sequences and 3 periods.
Defaults to "2x3x3". Details are given the section about Designs.

regulator   Regulatory settings for RSABE.
                   May be given as character from the choices "EMA" or "FDA" or as an object of
                   class 'regSet' (see [reg_const]).
                   Defaults to regulator="FDA" if missing.
                   This argument may be given also in lower case if given as character.

                   Also the linearized scaled ABE criterion is usually calculated with the FDA
                   constant r_const=log(1.25)/0.25 you can override this behavior to use the
                   EMA setting r_const=0.76 to avoid the discontinuity at CV=30% and be more
                   stringent.

nsims   Number of simulations to be performed to obtain the empirical power. Defaults
                   to 100,000 = 1e+5.
                   If simulations are aimed for empirical alpha nsims=1e+06 is recommended.

details   If set to TRUE the computational time is shown as well as the components for the
                   BE decision.
                   p(BE-sABEc) is the probability that the 95% CI of the ABE criterion is <0.
                   p(BE-PE) is the probability that the point estimate is within theta1 ... theta2.
                   p(BE-ABE) is the simulated probability for the conventional ABE test given for
                   comparision purposes.

setseed   Simulations are dependent on the starting point of the (pseudo) random number
                   generator. To avoid differences in power for different runs a set.seed() is
                   issued if setseed=TRUE, the default.

Details

The linearized scaled ABE criterion is calculated according to the SAS code given in the FDA's
progesterone guidance.
The simulations are done via the distributional properties of the statistical quantities necessary for
deciding BE based on scaled ABE criterion.
Details can be found in a document Implementation_scaledABE_simsVx.yy.pdf located in the
/doc sub-directory of the package.
If a CVcap is defined for the regulator, the BE decision is based on the inclusion of the CI in the
capped widened acceptance limits in case of CVwR > CVcap. This resembles method 'Howe-EMA'
in Muñoz *et al.* and is the standard behavior now if regulator="EMA" is choosen.

Value

Returns the value of the (empirical) power if argument details=FALSE.
Returns a named vector if argument details=TRUE.
p(BE) is the power, p(BE-sABEc) is the power of the scaled ABE criterion alone and p(BE-pe) is
the power of the criterion 'point estimat within acceptance range' alone.
p(BE-ABE) is the power of the conventional ABE test given for comparative purposes.

Designs

Although some designs are more 'popular' than others, power calculations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

In case of the design "2x2x3"" heteroscedasticity (*i.e.*, CVwT != CVwR) may lead to poor agreement of the power values compared to those calculated via the 'classical' way of subject data simulations if the design is unbalanced in respect to the number of subjects in the sequence groups. Therefore, the function issues a warning for that cases.

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Progesterone.* Recommended Apr 2010. Revised Feb 2011. download

Tóthfalusi, L, Endrényi, L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open access

Tóthfalusi L, Endrényi L, García Arieta A. *Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence.* Clin Pharmacokin. 2009;48(11):725–43. doi:10.2165/11318040-00000000000000

Muñoz J, Alcaide D, Ocaña J. *Consumer's risk in the EMA and FDA regulatory approaches for bioequivalence in highly variable drugs.* Stat Med. 2015;35(12):1933–43. doi:10.1002/sim.6834

See Also

sampleN.RSABE, power.scABEL

Examples

```
# using all the defaults:
# design="2x3x3" = partial replicate
# ABE limits, PE constraint 0.8-1.25
# true ratio = 0.90, 1E+5 simulations
power.RSABE(CV = 0.4, n = 36)
# should give
# [1] 0.83634
#
# to explore the simulation error due to the state of the
```

```
# random number generator
power.RSABE(CV = 0.4, n = 36, setseed = FALSE)
# will give something like
# [1] 0.83725
#
# explore pure RSABE (without mixed method, without pe constraint)
rs           <- reg_const("FDA")
rs$CVswitch  <- 0
rs$pe_constr <- FALSE
power.RSABE(CV = 0.4, n = 36, regulator = rs)
# should give
# [1] 0.84644
```

---

power.RSABE2L.sdsims   *(Empirical) Power of BE Decision via Reference Scaled ABE*

Description

These function performs the power calculation of the BE decision via the reference scaled ABE based on **subject data** simulations. Implemented are the methods ABEL, Hyslop and 'exact' as described in the references.

The estimation method of the key statistics needed to perform the RSABE decision is the usual ANOVA.

Usage

```
power.RSABE2L.sdsims(alpha = 0.05, theta1, theta2, theta0, CV, n,
                     design = c("2x3x3", "2x2x4", "2x2x3"), design_dta = NULL,
                     SABE_test = "exact", regulator, nsims = 1e+05,
                     details = FALSE, setseed = TRUE, progress)
```

Arguments

alpha	Type I error probability, significance level. Conventionally mostly set to 0.05.
theta1	Conventional lower ABE (Average Bioequivalence) limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).
	• If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR).

- If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].

n   Number of subjects under study.

May be given as vector. In that case it is assumed that n contains the number of subjects in the sequence groups.

If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown (showing the numbers of subjects in sequence groups).

Attention! In case of the "2x2x3" (TRT|RTR) design the order of sample sizes per sequence is important if given as vector. n[1] is for sequence group 'TRT' and n[2] is for sequence group 'RTR'.

design   Design of the study.

"2x3x3" is the partial replicate design.

"2x2x4" is a full replicate design with 2 sequences and 4 periods.

"2x2x3" is a full replicate design with 2 sequences and 3 periods.

Defaults to design="2x3x3". Details are given the section about Designs.

design_dta Alternatively to using the arguments design and n the design may be defined via a data.frame with columns subject, sequence, period and tmt. This feature is experimental in the sense that the data.frame is not checked for complying with the assumed structure.

If you use the argument design_dta you don't need to specify the arguments design and n.

The default design_dta=NULL means that design and n are used for the internal construction of the design data.frame.

SABE_test This argument specifies the test method to be used for the reference scaled ABE decision.

Default is the "exact" 'ncTOST' method of the two Laszlós. Other choices are "ABEL", "hyslop" and "fda". See Details.

regulator Regulatory settings for the widening of the BE acceptance limits.

May be given as character "EMA" or as an object of class 'regSet' (see [reg_const](#)). Defaults to regulator="EMA" if missing.

This argument may be given also in lower case if given as character.

If given as object of class 'regSet' the component est_method can not be "ISC".

nsims   Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+05.

If simulations are aimed for empirical alpha nsims=1e+06 is recommended.

details   If set to TRUE the computational time is shown as well as the components for the BE decision.

p(BE-RSABE) is the probability of a positive outcome of the SABE test.

p(BE-PE) is the probability that the point estimate is within theta1 ... theta2.

p(BE-ABE) is the simulated probability for the conventional ABE test.

setseed   Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed() is issued if setseed=TRUE, the default.

progress   Should a progressbar be shown? Defaults to `TRUE` if missing and `nsims` `>5e5`.

Details

The methods rely on the analysis of log-transformed data, *i.e.*, assumes a log-normal distribution on the original scale.

The data.frame with columns `subject`, `sequence`, `period` and `tmt` necessary for evalution of simulated subject data is constructed internally from the arguments `design` and `n` or may be given user defined via the argument `design_dta`. The last option is usefull if missing data have to be considered or if designs have to be evaluated which are not in the list of argument `design`.

The estimation method for obtaining the statistics necessary to perform the reference scaled ABE decision is the usual ANOVA with effects treatment, period, sequence and subject within sequence for the evaluation of all data and period, sequence and subject within sequence for the evaluation of the Reference formulation data only.

The SABE tests implemented are:

`"exact"`	'exact' based method of the two Laszlós (see references, called there 'ncTOST')
`"ABEL"`	Average bioequivalence with expanding limits
`"hyslop"`	BE decision via the linearized RSABE criterion and its upper 95% CI
`"fda"`	Hyslop with an additional bias correction term as implemented in the SAS code of the FDA's Guidance on Progesterone.

Value

Returns the value of the (empirical) power if argument `details=FALSE`.

Returns a named vector if argument `details=TRUE`.
`p(BE)` is the power, `p(BE-RSABE)` is the power of using the reference scaled ABE alone, and `p(BE-pe)` is the power of the criterion 'point estimate within acceptance range' alone. `p(BE-ABE)` is the power of the conventional ABE test given for comparative purposes.

Designs

Although some designs are more 'popular' than others, power calculations are valid for *all* of the following designs:

`"2x2x4"`	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
`"2x2x3"`	TRT | RTR
	TRR | RTT
`"2x3x3"`	TRR | RTR | RRT

Note

The function is relatively slow. The run-time for 1 Mio. simulations is between ~ 1 up to 6 minutes for n=12 or n=120 and 1 Mio. sim's (see the call under examples) on a machine with an Intel core i7 processor.

Thus be patient and go for a cup of coffee if you use this function with higher sample sizes and aim for estimating the type 1 error!

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Progesterone.* Recommended Apr 2010. Revised Feb 2011. download

Tóthfalusi L, Endrényi L. *An Exact Procedure for the Evaluation of Reference-Scaled Average Bioequivalence.* AAPS J. 2016;18(2):476–89. doi:10.1208/s1224801698736.

Tóthfalusi L, Endrényi L. *Algorithms for evaluating reference scaled average bioequivalence: power, bias, and consumer risk.* Stat Med. 2017;36(27):4378–4390. doi:10.1002/sim.7440

See Also

power.RSABE, reg_const

Examples

```
# Not run due to timing policy of CRAN

# pure EMA settings without mixed procedure, cap on widening and PE constraint
# as in the reference from 2017
reg           <- reg_const("EMA")
reg$CVswitch  <- 0
reg$CVcap     <- Inf
reg$pe_constr <- FALSE
reg$name      <- "EMA pure"
power.RSABE2L.sds(CV = 0.4, n = 12, theta0 = exp(0.05),
                  design = "2x2x4", regulator = reg, nsims = 50000)
# should give:
# [1] 0.46504 (compared to 47.1% in the 2017 reference)
```

---

power.scABEL   *(Empirical) Power of BE decision via scaled (widened) BE acceptance limits*

Description

These function performs the power calculation of the BE decision via scaled (widened) BE acceptance limits by simulations.

Usage

```
power.scABEL(alpha = 0.05, theta1, theta2, theta0, CV, n,
             design = c("2x3x3", "2x2x4", "2x2x3"), regulator,
             nsims, details = FALSE, setseed = TRUE)
```

Arguments

alpha	Type I error probability, significance level. Conventionally mostly set to 0.05.
theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). • If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR). • If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
n	Number of subjects under study. May be given as vector. In that case it is assumed that n contains the number of subjects in the sequence groups. If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown showing the numbers of subjects in sequence groups. Attention! In case of the "2x2x3" (TRT|RTR) design the order of sample sizes is important if given as vector. n[1] is for sequence group 'TRT' and n[2] is for sequence group 'RTR'.
design	Design of the study. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods. "2x2x3" is a full replicate design with 2 sequences and 3 periods. Defaults to "2x3x3". Details are given the section about Designs.
regulator	Regulatory settings for the widening of the BE acceptance limits. May be given as character from the choices "EMA", "HC", "FDA", "GCC" or as an object of class 'regSet' (see [reg_const](#)). Defaults to regulator="EMA" if missing. This argument may be given also in lower case if given as character.
nsims	Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+05.

	If not given and theta0 equals one of the expanded limits (*i.e.*, simulating empirical alpha), defaults to 1e+06.
details	If set to TRUE the computational time is shown as well as the components for the BE decision. p(BE-wABEL) is the probability that the CI is within (widened) limits. p(BE-PE) is the probability that the point estimate is within theta1 ... theta2. p(BE-ABE) is the simulated probability for the conventional ABE test.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed() is issued if setseed=TRUE, the default.

Details

The methods rely on the analysis of log-transformed data, *i.e.*, assume a log-normal distribution on the original scale.

The widened BE acceptance limits will be calculated by the formula
[L, U] = exp(-/+ r_const * sWR)
with r_const the regulatory constant and sWR the standard deviation of the within subjects variability of the Reference. r_const = 0.76 (~log(1.25)/0.29356) is used in case of regulator="EMA" or regulator="HC" and in case of regulator="FDA" r_const = 0.89257... (log(1.25)/0.25). If the CVwR of the Reference is < CVswitch=0.3 the conventional ABE limits apply (mixed procedure).

In case of regulator="EMA" a cap is placed on the widened limits if CVwR>0.5, *i.e.*, the widened limits are held at value calculated for CVwR=0.5. In case of regulator="HC" the capping is done such that the acceptance limits are 0.6666 ... 1.5 at maximum.

The case of regulator="GCC" is treatd as special case of ABEL with CVswitch = CVcap = 0.3. The r_const = log(1.25)/CV2se(0.3) assures that for CV>0.3 the widened BE limits of 0.7 ... 1.3333 are used.

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on widened ABEL.
For more details see the document Implementation_scaledABE_simsVx.yy.pdf in the /doc subdirectory of the package.

Function power.scABEL() implements the simulation via distributional characteristics of the 'key' statistics obtained from the EMA recommended evaluation via ANOVA if regulator="EMA" or if the regulator component est_method is set to "ANOVA" if regulator is an object of class 'regSet'. Otherwise the simulations are based on the distributional characteristis of the 'key' statistics obtained from evaluation via intra-subject contrasts (ISC), as recommended by the FDA.

Value

Returns the value of the (empirical) power if argument details=FALSE.

Returns a named vector if argument details=TRUE.
p(BE) is the power, p(BE-ABEL) is the power of the widened ABEL criterion alone and p(BE-pe) is

the power of the criterion 'point estimate within acceptance range' alone. p(BE-ABE) is the power of the conventional ABE test given for comparative purposes.

Designs

Although some designs are more 'popular' than others, power calculations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

Cross-validation of the simulations as implemented here and via the 'classical' subject data simulation have shown somewhat unsatisfactory results for the 2x3x3 design if the variabilities for Test and Reference are different and/or sequences exteremly unbalanced.
The function power.scABEL() therefore gives a warning if calculations with different CVwT and CVwR are requested for the 2x3x3 partial replicate design. For "EMA" subject simulations are provided in power.scABEL.sdsims. For more details see the above mentioned document Implementation_scaledABE_simsVy

Note

In case of regulator="FDA" the (empirical) power is only approximate since the BE decision method is not exactly what is expected by the FDA. But the "Two Laszlós" state that the scABEL method should be 'operational equivalent' to the FDA method.
To get the power for the FDA favored method via linearized scaled ABE criterion use function power.RSABE.

In case of regulator="HC" (based on ISC), power is also only approximative since Health Canada recommends an evaluation via mixed model approach. This could only implemented via subject data simulations which are very time consuming. But ISC may be a good substitute.

Author(s)

D. Labes

References

Tóthfalusi L, Endrényi L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open source

See Also

sampleN.scABEL, power.RSABE, reg_const

Examples

```
# using all the defaults:
# design="2x3x3", EMA regulatory settings
# PE constraint 0.8-1.25, cap on widening if CV>0.5
# true ratio=0.90, 1E+6 simulations
power.scABEL(CV = 0.4, n = 29)
# should give:
# Unbalanced design. n(i)=10/10/9 assumed.
# [1] 0.66113
#
# with details=TRUE to view the computational time and components
power.scABEL(CV = 0.5, n = 54, theta0 = 1.15, details = TRUE)
# should give (times may differ depending on your machine):
# 1e+05sims. Time elapsed (sec): 0.07
#
#      p(BE) p(BE-wABEL)    p(BE-pe)   p(BE-ABE)
#    0.81727     0.82078     0.85385     0.27542
#
# exploring 'pure ABEL' with the EMA regulatory constant
# (without mixed method, without capping, without pe constraint)
rs            <- reg_const("EMA")
rs$CVswitch  <- 0
rs$CVcap     <- Inf
rs$pe_constr <- FALSE
power.scABEL(CV = 0.5, n = 54, theta0 = 1.15, regulator = rs)
# should give
# [1] 0.8519
```

---

power.scABEL.sds   *(Empirical) Power of BE decision via scaled (widened) BE acceptance*
                            limits

Description

These function performs the power calculation of the BE decision via scaled (widened) BE acceptance limits based on **subject data** simulations.
This function has an alias power.scABEL.sds().

Usage

```
power.scABEL.sdsims(alpha = 0.05, theta1, theta2, theta0, CV, n,
                    design = c("2x3x3", "2x2x4", "2x2x3"), design_dta=NULL,
                    regulator, nsims = 1e+05, details = FALSE, setseed = TRUE,
                    progress)
```

Arguments

alpha   Type I error probability, significance level. Conventionally mostly set to 0.05.

theta1	Conventional lower ABE limit to be applied in the mixed procedure if `CVsWR <= CVswitch`. Also lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if `CVsWR <= CVswitch`. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). - If given as a scalar (`length(CV)==1`) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR). - If given as a vector (`length(CV)==2`), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in `CV[1]` and the one of the Reference in the `CV[2]`.
n	Number of subjects under study. May be given as vector. In that case it is assumed that n contains the number of subjects in the sequence groups. If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown showing the numbers of subjects in sequence groups. Attention! In case of the `"2x2x3"` (TRT|RTR) design the order of sample sizes is important if given as vector. `n[1]` is for sequence group 'TRT' and `n[2]` is for sequence group 'RTR'.
design	Design of the study to be planned. `"2x3x3"` is the partial replicate design (TRR|RTR|RRT). `"2x2x4"` is the full replicate design with 2 sequences and 4 periods. `"2x2x3"` is the 3-period design with sequences TRT|RTR. Defaults to `design="2x3x3"`.
design_dta	Alternatively to using the arguments `design` and `n` the design may be defined via a data.frame with columns `subject`, `sequence`, `period` and `tmt`. This feature is experimental in the sense that the data.frame is not checked for complying with the assumed structure. If you use the argument `design_dta` you don't need to specify the arguments `design` and `n`. The default `design_dta = NULL` means that `design` and `n` are used for the internal construction of the design data.frame.
regulator	Regulatory settings for the widening of the BE acceptance limits. May be given as `"EMA"` or as an object of class 'regSet' (see [reg_const](#)). Defaults to `regulator="EMA"` if missing. This argument may be given also in lower case if given as character. If given as object of class 'regSet' the component `est_method` must not be `"ISC"`.
nsims	Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+05. If simulations are aimed for empirical alpha nsims=1e+06 is recommended.

details	If set to TRUE the computational time is shown as well as the components for the BE decision.
	p(BE-wABEL) is the probability that the CI is within (widened) limits.
	p(BE-PE) is the probability that the point estimate is within theta1 ... theta2.
	p(BE-ABE) is the simulated probability for the conventional ABE test.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed() is issued if setseed=TRUE, the default.
progress	Should a progressbar be shown? Defaults to TRUE if missing and nsims >5E5.

Details

The methods rely on the analysis of log-transformed data, *i.e.*, assume a log-normal distribution on the original scale.

The widened BE acceptance limits will be calculated by the formula
[L, U] = exp(± r_const * sWR)
with r_const the regulatory constant and sWR the standard deviation of the within subjects variability of the Reference. r_const = 0.76 (~log(1.25)/0.29356) is used in case of regulator="EMA". If the CVwR of the Reference is < CVswitch=0.3 the conventional ABE limits apply (mixed procedure).
In case of regulator="EMA" a cap is placed on the widened limits if CVwr>0.5, *i.e.*, the widened limits are held at value calculated for CVwR=0.5.

The simulations are done by simulating subject data (all effects fixed except the residuals) and evaluating these data via ANOVA of all data to get the point estimate of T vs. R along with its 90% CI and an ANOVA of the data under R(eference) only to get an estimate of s2wR.
The data.frame with columns subject, sequence, period and tmt necessary for evalution of simulated subject data is constructed internally from the arguments design and n or may be given user defined via the argument design_dta. The last option is usefull if missing data have to be considered or if designs have to be evaluated which are not in the list of argument design.
This feature is experimental in the sense that the data.frame is not checked for complying with the assumed structure.

Value

Returns the value of the (empirical) power if argument details=FALSE.

Returns a named vector if argument details=TRUE.
p(BE) is the power, p(BE-wABEL) is the power of the widened ABEL criterion alone and p(BE-pe) is the power of the criterion 'point estimat within acceptance range' alone. p(BE-ABE) is the power of the conventional ABE test given for comparative purposes.

Note

The function is mainly intended for crosscheck of power.scABEL() results.
But may be mandatory for cases where power.scABEL() results are inaccurate (low sample sizes and/or heteroscedasticity).
It is relatively slow. The run-time of this function doing 1 Mio sims is between ~ 7-8 sec for n=12

and ~ 3-4 min for n=120 on a machine with an Intel core i7 processor.
Thus be patient and go for a cup of coffee if you use this function with high sample sizes!

Author(s)

D. Labes, B. Lang

References

Tóthfalusi L, Endrényi L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open source

See Also

power.scABEL, reg_const

Examples

```
# using all the defaults:
# design="2x3x3", EMA regulatory settings
# PE constraint 0.8-1.25, cap on widening if CV>0.5
# true ratio=0.90, 1E+5 simulations
power.scABEL.sdsims(CV = 0.4, n = 36)
# should give:
# [1] 0.74321
```

power.TOST   *Power of the classical TOST procedure*

Description

Calculates the exact or approximate power of the two-one-sided t-tests (TOST) procedure for various study designs used in BE studies.

Usage

```
power.TOST(alpha = 0.05, logscale = TRUE, theta1, theta2, theta0, CV, n,
           design = "2x2", method="exact", robust=FALSE)
```

Arguments

alpha	Significance level (one-sided). Commonly set to 0.05.
logscale	Should the data used on log-transformed or on original scale? TRUE (default) or FALSE.

theta0   'True' or assumed T/R ratio or difference.

In case of `logscale=TRUE` it must be given as ratio T/R.

If `logscale=FALSE`, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of CV, `theta1` and `theta2` need also be given relative to the reference mean (specified as ratio).

Defaults to 0.95 if `logscale=TRUE` or to 0.05 if `logscale=FALSE`

theta1   Lower (bio-)equivalence limit.

In case of `logscale=TRUE` it is given as ratio.

If `logscale=FALSE`, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, `theta0` and `theta2` need also be given relative to the reference mean (specified as ratio).

Defaults to 0.8 if `logscale=TRUE` or to -0.2 if `logscale=FALSE`.

theta2   Upper (bio-)equivalence limit.

In case of `logscale=TRUE` it is given as ratio. If `logscale=FALSE`, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, `theta0` and `theta1` need also be given relative to the reference mean (specified as ratio).

If not given, `theta2` will be calculated as 1/theta1 if `logscale=TRUE` or as -theta1 if `logscale=FALSE`.

CV   In case of `logscale=TRUE` the (geometric) coefficient of variation given as ratio. If `logscale=FALSE` the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of `theta0`, `theta1` and `theta2` need also be given relative to the reference mean (specified as ratio).

In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.

n   Number of subjects under study.

Is total number if given as scalar, else number of subjects in the (sequence) groups. In the latter case the length of n vector has to be equal to the number of (sequence) groups.

design   Character string describing the study design.

See `known.designs()` for designs covered in this package.

method   Method for calculation of the power.

Defaults to `"exact"` in which case the calculation is done based on formulas with Owen's Q. The calculation via Owen's Q can also be choosen with `method="owenq"`.

Another exact method via direct integration of the bivariate non-central *t*-distribution may be chosen with `method="mvt"`. This may have somewhat lower precision compared to Owen's Q and longer run-time.

Approximate calculations can be choosen via `method="noncentral"` or `method="nct"`

for the approximation using the non-central *t*-distribution. With `method="central"` or `method="shifted"` the relative crude approximation via 'shifted' central *t*-distribution is chosen.

The strings for `method` may be abbreviated.

robust   Defaults to `FALSE`. With that value the usual degrees of freedom will be used. Set to `TRUE` will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as `n-seq`. See `known.designs()$df2` for designs covered in this package.

Has only effect for higher-order crossover designs.

Details

The exact calculations of power are based on Owen's Q-function or by direct integration of the bivariate non-central *t*-distribution via function [pmvt] of package mvtnorm.

Approximate power is implemented via the non-central *t*-distribution or the 'shifted' central *t*-distribution.

The formulas cover balanced and unbalanced studies w.r.t (sequence) groups.

In case of parallel group design and higher order crossover designs (replicate crossover or crossover with more than two treatments) the calculations are based on the assumption of equal variances for Test and Reference products under consideration.

The formulas for the paired means 'design' do not take a correlation parameter into account. They are solely based on the paired *t*-test (TOST of differences = zero).

Value

Value of power according to the input arguments.

Note

Of course it is highly recommended to use the default `method="exact"` :-).

There is no reason beside testing and for comparative purposes to use an approximation if the exact method is available.

If n is given as scalar (total sample size) and this number is not divisible by the number of (sequence) groups of the design an unbalanced design with small imbalance is assumed. A corresponding message is thrown showing the assumed numbers of subjects in (sequence) groups.

The function does not vectorize properly if design is a vector.

The function vectorizes properly if CV or theta0 are vectors.

Other vector input is not tested yet.

The former function `power2.TOST()` designd to handle unbalanced studies is defunct since `power.TOST()` handles balanced as well as unbalanced designs.

Author(s)

D. Labes, direct integration of bivariate non-central *t*-distribution by B. Lang

References

Phillips KF. *Power of the Two One-Sided Tests Procedure in Bioequivalence.* J Pharmacokin Biopharm. 1990;18(2):137–44. doi:10.1007/BF01063556

Diletti D, Hauschke D, Steinijans VW. *Sample Size Determination for Bioequivalence Assessment by Means of Confidence Intervals.* Int J Clin Pharmacol Ther Toxicol. 1991;29(1):1–8.

See Also

sampleN.TOST, known.designs

Examples

```
# power for the 2x2 cross-over design with 24 subjects and CV 25%
# using all the other default values
power.TOST(CV = 0.25, n = 24)
# should give: [1] 0.7391155
# nct approximation very good for this configuration
power.TOST(CV = 0.25, n = 24, method = "nct")
# gives also: [1] 0.7391155
# shifted-central-t  approximation
power.TOST(CV = 0.25, n = 24, method = "shifted")
# gives:      [1] 0.7328894

# power for the 2x2 cross-over study with 24 subjects, CV 25%
# and 2 drop-outs in the same sequence group (unbalanced study)
power.TOST(CV=0.25, n=c(10,12))
# should give: [1] 0.6912935
# not the same compared to the balanced setting
power.TOST(CV=0.25, n=22)
# should give: [1] 0.6953401
```

---

power.TOST.sds	*Power calculation of the BE decision with models incorporating groups*

Description

The power is obtained via subject data simulations.
Three models are implemented:

- gmodel==1 is full FDA model for testing group-by-treatment interaction followed by gmodel==2 or gmodel==3 with data of the biggest group depending on the test of the treatment by group interaction
- gmodel==2 is full FDA model but without group-by-treatment interaction
- gmodel==3 is model with pooled groups, i.e. without any group term

Usage

```
power.TOST.sds(alpha = 0.05, theta1, theta2, theta0, CV, n,
               design = c("2x2", "2x2x2", "2x3x3", "2x2x4", "2x2x3"),
             design_dta = NULL, grps = 2, ngrp = NULL, gmodel = 2, p.level=0.1,
              nsims = 1e+05, details = FALSE, setseed = TRUE, progress)
```

Arguments

alpha	Type I error probability, significance level. Conventionally mostly set to 0.05.
theta1	Lower BE limit. Defaults to 0.8 if not given explicitely.
theta2	Upper BE limit. Defaults to 1.25 if not given explicitely.
theta0	'True' or assumed T/R ratio. Defaults to 0.95 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). • If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR). • If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
n	Number of subjects under study. May be given as vector. In that case it is assumed that n contains the number of subjects in the sequence groups. If n is given as single number (total sample size) and this number is not divisible by the number of sequences of the design an unbalanced design is assumed. A corresponding message is thrown showing the numbers of subjects in sequence groups. Attention! In case of the "2x2x3" (TRT|RTR) design the order of sample sizes is important if given as vector. n[1] is for sequence group 'TRT' and n[2] is for sequence group 'RTR'.
design	Design of the study to be planned. "2x2" or "2x2x2" is the conventional cross-over design. "2x3x3" is the partial replicate design (TRR|RTR|RRT). "2x2x4" is the full replicate design with 2 sequences and 4 periods. "2x2x3" is the 3-period design with sequences TRT|RTR. Defaults to design="2x2".
design_dta	Alternatively to using the arguments design and n the design may be defined via a data.frame with columns subject, sequence, period and tmt. This feature is experimental in the sense that the data.frame is not checked for complying with the assumed structure. If you use the argument design_dta you don't need to specify the arguments design and n. The default design_dta = NULL means that design and n are used for the internal construction of the design data.frame.
grps	Number of (logistical) groups. Defaults to 2.
ngrp	Vector of number of subjects in groups.

gmodel   Number describing the model incorporating group effects

- gmodel=1 is full FDA model for testing group-by-treatment interaction followed by gmodel=2 or gmodel=3 with data of the biggest group depending on the test of the treatment by group interaction
- gmodel=2 is full FDA model but without group-by-treatment interaction
- gmodel=3 is model with pooled groups, i.e. without any group term

Defaults to gmodel=2.

p.level   Significance level of the test of a group-by-treatment interaction. Defaults to p.level=0.1.

nsims   Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+05.
                If simulations are aimed for empirical alpha nsims=1e+06 is recommended.

details   If set to TRUE the computational time is shown.

setseed   Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(123456) is issued if setseed=TRUE, the default.

progress   Should a progressbar be shown? Defaults to TRUE if missing and nsims >5E5.

Details

The power is calculated via subject data sims.
The evaluation of BE is done via 1-2*alpha confidence interval using classical ANOVA for the models with group effects.
The data.frame with columns subject, sequence, period and tmt necessary for evaluation of simulated subject data is constructed internally from the arguments design and n or may be given user defined via the argument design_dta. The last option is usefull if missing data have to be considered or if designs have to be evaluated which are not in the list of argument design.
This feature is experimental in the sense that the data.frame is not checked for complying with the assumed structure.

The p.value of the test of the group-by-treatment interaction in case of gmodel=1
defaults to p.level = 0.1, the value originally used by the FDA. Later on a value of p.level = 0.05 was used.

If the group-by-treatment interaction is significant the subsequent BE decision is done with the data of the largest group. If there are more than one with the same size, one gets a warning that this feature – showing BE in all that groups – is not implemented yet. Only the first of the largest groups is tested for BE.

Value

Returns the value of the (empirical) power

Note

The run time of the function may be relatively long.
Take a cup of coffee and be patient.

Author(s)

D. Labes

References

Schütz H.
Multi-Group Studies in Bioequivalence. To pool or not to pool?
Presentation at BioBriges 2018, Prague. <https://bebac.at/lectures/Prague2018.pdf>

Examples

```
# power for gmodel=2, 2x2 crossover, grps=3 with even number of subjects
power.TOST.sds(CV=0.2, n=18, grps=3)
# gives [1] 0.78404
# without considering groups
power.TOST.sds(CV=0.2, n=18, gmodel=3)
# gives [1] 0.7887
```

---

power.TOST.sim   *Power of the TOST procedure obtained via simulations*

Description

Power is calculated by simulations of studies (PE via its normal distribution, MSE via its associated χ^2 distribution) and application of the two one-sided *t*-tests. Power is obtained via ratio of studies found BE to the number of simulated studies.

Usage

```
power.TOST.sim(alpha = 0.05, logscale = TRUE, theta1, theta2, theta0, CV, n,
               design = "2x2", robust = FALSE, setseed = TRUE, nsims = 1e+05)
```

Arguments

alpha	Significance level (one-sided). Commonly set to 0.05.
logscale	Should the data used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	'True' or assumed T/R ratio or difference. In case of logscale=TRUE it must be given as ratio T/R. If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of CV, theta1 and theta2 need also be given relative to the reference mean (specified as ratio). Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE

theta1   Lower (bio-)equivalence limit.
                In case of `logscale=TRUE` it is given as ratio.
                If `logscale=FALSE`, the limit may be expressed in two ways: difference of
                means relative to the same (underlying) reference mean or in units of the dif-
                ference of means. Note that in the former case the units of `CV`, `theta0` and
                `theta2` need also be given relative to the reference mean (specified as ratio).
                Defaults to 0.8 if `logscale=TRUE` or to -0.2 if `logscale=FALSE`.

theta2   Upper (bio-)equivalence limit.
                In case of `logscale=TRUE` it is given as ratio. If `logscale=FALSE`, the limit may
                be expressed in two ways: difference of means relative to the same (underlying)
                reference mean or in units of the difference of means. Note that in the former
                case the units of `CV`, `theta0` and `theta1` need also be given relative to the refer-
                ence mean (specified as ratio).
                If not given, `theta2` will be calculated as `1/theta1` if `logscale=TRUE` or as
                `-theta1` if `logscale=FALSE`.

CV   In case of `logscale=TRUE` the (geometric) coefficient of variation given as ratio.
                If `logscale=FALSE` the argument refers to (residual) standard deviation of the
                response. In this case, standard deviation may be expressed two ways: relative
                to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of
                variation; or untransformed, i.e. as standard deviation of the response. Note that
                in the former case the units of `theta0`, `theta1` and `theta2` need also be given
                relative to the reference mean (specified as ratio).

                In case of cross-over studies this is the within-subject CV, in case of a parallel-
                group design the CV of the total variability.

n   Number of subjects under study.
                Is total number if given as scalar, else number of subjects in the (sequence)
                groups. In the latter case the length of n vector has to be equal to the number of
                (sequence) groups.

design   Character string describing the study design.
                See `known.designs()` for designs covered in this package.

robust   Defaults to `FALSE`. With that value the usual degrees of freedom will be used.
                Set to `TRUE` will use the degrees of freedom according to the 'robust' evaluation
                (aka Senn's basic estimator). These degrees of freedom are calculated as n−seq.
                See `known.designs()$df2` for designs covered in this package.
                Has only effect for higher-order crossover designs.

setseed   Simulations are dependent on the starting point of the (pseudo) random number
                generator. To avoid differences in power for different runs a `set.seed(1234567)`
                is issued if `setseed=TRUE`, the default.
                Set this argument to `FALSE` to view the variation in power between different runs.

nsims   Number of studies to simulate. Defaults to 100,000 = 1E5.

Value

Value of power according to the input arguments.

Note

This function was intended for internal check of the analytical power calculation methods. Use of the analytical power calculation methods (power.TOST()) for real problems is recommended. For sufficient precision nsims > 1E5 (default) may be necessary. Be patient if using nsims=1E6. May take some seconds.

Author(s)

D. Labes

See Also

power.TOST,

Examples

```
# using the default design 2x2, BE range 0.8 ... 1.25, logscale, theta0=0.95
power.TOST.sim(alpha = 0.05, CV = 0.3, n = 12)
# should give 0.15054, with nsims=1E6 it will be 0.148533
# exact analytical is
power.TOST(alpha = 0.05, CV = 0.3, n = 12)
# should give 0.1484695

# very unusual alpha setting
power.TOST.sim(alpha = 0.9, CV = 0.3, n = 12)
# should give the same (within certain precision) as
power.TOST(alpha = 0.95, CV = 0.3, n = 12)
# or also within certain precision equal to
power.TOST(alpha = 0.95, CV = 0.3, n = 12, method = "mvt")
# SAS Proc Power gives here the incorrect value 0.60525
```

---

  pvalue.TOST   *p-value(s) of the TOST procedure*

Description

Calculates the *p*-value(s) of the TOST procedure via students *t*-distribution given pe, CV and n.

Usage

```
pvalue.TOST(pe, CV, n, logscale = TRUE, theta1, theta2, design = "2x2",
            robust = FALSE, both = FALSE)
pvalues.TOST(pe, CV, n, logscale = TRUE, theta1, theta2, design = "2x2",
             robust = FALSE, both = TRUE)
```

Arguments

pe	Observed point estimate of the T/R ratio or difference. In case of logscale=TRUE it must be given as ratio T/R. If logscale=FALSE, the observed difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of CV, theta1 and theta2 need also be given relative to the reference mean (specified as ratio).
CV	In case of logscale=TRUE the observed (geometric) coefficient of variation given as ratio. If logscale=FALSE the argument refers to the observed (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of pe, theta1 and theta2 need also be given relative to the reference mean (specified as ratio). In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.
n	Total number of subjects if given as scalar. Number of subjects in (sequence) groups if given as vector.
logscale	Should the data be used after log-transformation or on original scale? TRUE or FALSE. Defaults to TRUE.
theta1	Lower (bio-)equivalence limit. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, pe and theta2 need also be given relative to the reference mean (specified as ratio). Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
theta2	Upper (bio-)equivalence limit. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV, theta0 and theta1 need also be given relative to the reference mean (specified as ratio). If not given, theta2 will be calculated as 1/theta1 if logscale=TRUE or as -theta1 if logscale=FALSE.
design	Character string describing the study design. See known.designs() for designs covered in this package.
robust	If set to TRUE triggers the use of degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as n-seq. See known.designs()$df2. Has only effect for higher-order crossover designs. Defaults to FALSE. With that value the usual degrees of freedom will be used.

both   Indicates if both *p*-values (*t*-tests of pe >= theta1 and pe <= theta2) shall be given
                        back or only the maximum.
                        Defaults to `FALSE` for the function `pvalue.TOST()` and to `TRUE` for the function
                        `pvalues.TOST()`.

Value

Returns the *p*-value(s).
Returns a vector with named elements `p.left`, `p.right` if arguments pe and CV are scalars, else a
matrix with columns `p.left`, `p.right`.
`p.left` gives the *p*-value of testing
`HA1: theta >= theta1`
and `p.right` the *p*-value of testing
`HA2: theta <= theta2`
against their respective Nulls.

Note

The formulas implemented cover balanced and unbalanced designs.

In case of argument n given as n(total) and is not divisible by the number of (sequence) groups
the total sample size is partitioned to the (sequence) groups to have small imbalance only. A message is given in such cases.

SAS procedure TTEST with the TOST option names p.left = Upper, p.right= Lower according
to the tail of the *t*-distribution to be used for obtaining the *p*-values.

Author(s)

B. Lang, man page by D. Labes

References

Schuirmann DJ. *A comparison of the two one-sided tests procedure and the power approach for
assessing the equivalence of average bioavailability.* J Pharmacokin Biopharm. 1987;15:657–80.
[doi:10.1007/BF01068419](doi:10.1007/BF01068419)

Hauschke D, Steinijans V, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester:
Wiley; 2007.

See Also

[CI.BE](CI.BE)

Examples

```
# Defaults: 2x2 crossover, log-transformation
# BE acceptance limits 0.8 ... 1.25, usual dfs
# interested in both p-values
pvalues.TOST(pe = 0.95, CV = 0.3, n = 12)
# gives the vector (named elements)
```

```
#     p.left    p.right
# 0.09105601 0.02250985
# i.e. 'left' hypothesis H01: theta<=theta1 can't be rejected
# 'right' hypothesis H02: theta>=theta2 can be rejected

# max. p-value only as 'overall' pvalue, preferred by Benjamin
pvalue.TOST(pe = 0.912, CV = 0.333, n = 24)
# should give 0.08777621, i.e., inequivalence can't be rejected
# this is operationally identical to
CI.BE(pe = 0.912, CV = .333, n = 24)
# lower limit = 0.7766 outside 0.8 ... 1.25, i.e., inequivalence can't be rejected
```

---

reg_const	*Constructor of an object with class 'regSet' containing the regulatory settings for ABEL*

Description

This function may be used to define regulatory settings not implemented yet in PowerTOST.

Usage

```
reg_const(regulator, r_const, CVswitch, CVcap, pe_constr)
```

Arguments

regulator	Name of the regulatory body as a string. Implemented settings are for "EMA", "FDA", "HC", and "GCC". The former (inofficial) settings for "ANVISA" are covered by the EMA settings. In case of regulator="USER" the other arguments must be given. Otherwise, they may be missing.
r_const	Regulatory constant.
CVswitch	CV to switch to the widened acceptance limits.
CVcap	CV for capping the widening of the acceptance limits.
pe_constr	Logical. Shall pe constraint be applied? Defaults to TRUE.

Value

Returns an object of class 'regSet', a list with components

name	Name of the settings
CVswitch	see arguments
r_const	Regulatory constant
CVcap	see arguments
pe_constr	see arguments
est_method	"ANOVA" or "ISC"

Class 'regSet' has a S3 print method.

The component est_method is automatically set to "ANOVA", except for regulator="FDA" or regulator="HC" where "ISC" is used.

Note

The former inofficial regulatory settings for regulator="ANVISA" are covered by regulator="EMA" (BEBA Forum).

The settings for CVcap of Health Canada (regulator="HC") were chosen in such a way that the limits of the acceptance range are capped nearly exact to 1/1.5 up to 1.5. Literally it is given rounded to 3 significant digits.

Author(s)

D. Labes

References

BEBA Forum. May 2016. online

Health Canada, Therapeutic Products Directorate. *Comparative Bioavailability Standards: Formulations Used for Systemic Effects, 2.1.1.8 Highly variable drug products* Ottawa, 08 June 2018. online

Examples

```
# to retrieve the EMA settings
reg_const("EMA")
# to define the old ANVISA settings
reg       <- reg_const("USER", r_const = 0.76, CVswitch = 0.4, CVcap = 0.5)
reg$name <- "Old ANVISA"
# Use reg as argument in the scaled ABEL power / sample size functions for
```

---

sampleN.2TOST   *Sample size based on power of two TOSTs*

Description

Estimates the necessary sample size to have at least a given power when two parameters are tested simultaneously.

Usage

```
sampleN.2TOST(alpha = c(0.05, 0.05), targetpower = 0.8, logscale = TRUE,
              theta0, theta1, theta2, CV, rho, design = "2x2", setseed = TRUE,
              robust = FALSE, print = TRUE, details = FALSE, imax = 100,
              nsims = 1e+05)
```

Arguments

alpha	Vector; contains one-sided significance level for each of the two TOSTs. For one TOST, by convention mostly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
logscale	Should the data used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	Vector; contains 'true' assumed T/R ratio for each of the two TOSTs. In case of logscale=TRUE each element must be given as ratio, otherwise as difference to 1. See examples. Defaults to c(0.95, 0.95) if logscale=TRUE or to c(0.05, 0.05) if logscale=FALSE.
theta1	Vector; contains lower bioequivalence limit for each of the two TOSTs. In case of logscale=TRUE it is given as ratio, otherwise as diff. to 1. Defaults to c(0.8, 0.8) if logscale=TRUE or to c(-0.2, -0.2) if logscale=FALSE.
theta2	Vector; contains upper bioequivalence limit for each of the two TOSTs. If not given theta2 will be calculated as 1/theta1 if logscale=TRUE or as -theta1 if logscale=FALSE.
CV	Vector of coefficient of variations (given as as ratio, *e.g.*, 0.2 for 20%). In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability. In case of logscale=FALSE CV is assumed to be the respective standard deviation.
rho	Correlation between the two PK metrics (*e.g.*, AUC and Cmax) under consideration. This is defined as correlation between the estimator of the treatment difference of PK metric one and the estimator of the treatment difference of PK metric two. Has to be within $\{-1, +1\}$.
design	Character string describing the study design. See known.designs() for designs covered in this package.
setseed	Logical; if TRUE, the default, a seed of 1234567 is set.
robust	Defaults to FALSE. With that value the usual degrees of freedom will be used. Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These degrees of freedom are calculated as n-seq. See known.designs()$df2 for designs covered in this package. Has only effect for higher-order crossover designs.
print	If TRUE (default) the function prints its results. If FALSE only the result list will be returned.
details	If TRUE the design characteristics and the steps during sample size calculations will be shown. Defaults to FALSE.
imax	Maximum number of steps in sample size search. Defaults to 100.
nsims	Number of studies to simulate. Defaults to 100,000 = 1E5.

Details

The sample size is estimated via iterative evaluation of power of the two TOSTs.
Start value for the sample size search is taken from a large sample approximation (one TOST) according to Zhang, modified.
The sample size is bound to 4 as minimum.

The estimated sample size gives always the *total* number of subjects (not subject/sequence in crossovers or subjects/group in parallel designs – like in some other software packages).

Value

A list with the input and results will be returned.
The element name "Sample size" contains the total sample size.

Warning

The function does not vectorize properly.
If you need sample sizes with varying CVs, use f.i. for-loops or the apply-family.

Note

If both theta0 are near the acceptance limits then the starting value may not be a good approximation resulting in a lot of iteration steps; imax may need to be increased to obtain the required sample size.

Author(s)

B. Lang, D. Labes

References

Phillips KF. *Power for Testing Multiple Instances of the Two One-Sided Tests Procedure.* Int J Biostat. 2009;5(1):Article 15.

Hua SY, Xu S, D'Agostino RB Sr. *Multiplicity adjustments in testing for bioequivalence.* Stat Med. 2015;34(2):215–31. doi:10.1002/sim.6247

Lang B, Fleischer F. *Letter to the Editor: Comments on 'Multiplicity adjustments in testing for bioequivalence'.* Stat Med. 2016;35(14):2479–80. doi:10.1002/sim.6488

Zhang P. *A Simple Formula for Sample Size Calculation in Equivalence Studies.* J Biopharm Stat. 2003;13(3):529–538. doi:10.1081/BIP120022772

See Also

power.2TOST, known.designs

Examples

```
# Sample size for 2x2x2 cross-over design, intra-subject CV = 30% and assumed
# ratios of 0.95 for both parameters, and correlation 0.9 between parameters
# (using all the other default values)
# Should give n=44 with power=0.80879
sampleN.2TOST(theta0 = rep(0.95, 2), CV = rep(0.3, 2), rho = 0.9)

# Sample size for a parallel group design,
# evaluation on the original (untransformed) scale
# BE limits 80 ... 120% = -20% ... +20% of reference,
# assumed true BE ratio 0.95% = -5% to reference mean for both parameters,
# total CV=20% for both parameters, and correlation 0.9 between parameters
# should give n=52 with power=0.80094
sampleN.2TOST(logscale=FALSE, theta0 = rep(-0.05, 2), CV = c(0.2, 0.2),
              rho = 0.9, design = "parallel")
```

---

sampleN.dp	*Sample size estimation of dose-proportionality studies evaluated via the power model*

Description

Performs a sample size estimation for dose-proportionality studies using the power model for cossover (Latin square), parallel group designs or incomplete block designs via a confidence interval equivalence criterion.

Usage

```
sampleN.dp(alpha = 0.05, CV, doses, targetpower = 0.8, beta0, theta1 = 0.8,
           theta2 = 1/theta1, design = c("crossover", "parallel", "IBD"),
           dm=NULL, CVb, print = TRUE, details = FALSE, imax = 100)
```

Arguments

alpha	Type 1 error. Usually set to 0.05.
CV	Coefficient of variation. Is intra-subject CV for design="crossover" and CV of total variability in case of design="parallel"
doses	Vector of dose values under study. At least two doses have to be given.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
beta0	'True' or assumed slope of the power model. If missing defaults to 1+log(0.95)/log(rd) where rd is the ratio is the ratio of the highest to the lowest dose. Has to be within slope acceptance range according to 1+log(theta1)/log(rd) and 1+log(theta2)/log(rd). Otherwise, the function issues an error.
theta1	Lower acceptance limit for the ratio of dose normalized means (Rdmn). Transformes into slope acceptance range as described under item beta0.

theta2	Upper acceptance limit for the ratio of dose normalized means (Rdmn).
design	Crossover design (default), parallel group design or incomplete block design (IBD).
	Crossover design means Latin square design with number of doses as dimension.
dm	'Design matrix' of the incomplete block design (IBD) if design="IBD".
	This matrix contains the sequences in rows and periods in columns. The entry (i, j) of the design matrix corresponds to the dose (index) a subject with i-th sequence gets in the j-th period. Can be obtained f.i. via functions of package crossdes. See examples.
	Function bib.CL returns some IBDs described by Chow & Liu.
CVb	Coefficient of variation of the between-subject variability.
	Only necessary if design="IBD". Will be set to 2*CV if missing. This is only a crude rule of thumb. Better obtain an estimate of CVb from a previous crossover study.
	Set CVb=0 if all-effects-fixed model shall be used. This model gives lower sample sizes than the mixed model with random subject effects (random intercept).
print	If TRUE (default) the function prints its results.
	If set to FALSE only the data.frame with the results will be returned.
details	If details=TRUE the steps during sample size search will be shown. Defaults to FALSE.
imax	Maximum number of steps in sample size search.
	Defaults to 100. Adaption only in rare cases needed, if any.

Details

The sample size is estimated via iterative evaluation of power.dp().
Start value for the sample size search is taken from a large sample approximation.
The sample size is bound to number of dose or sequence groups as minimum.
Balanced designs are used although this is not absolutely necessary.

The estimated sample size gives always the *total* number of subjects (not subject/sequence in crossovers or subjects/group in parallel designs – like in some other software packages).

Value

A data.frame with the input and results will be returned.
The Sample size column contains the total sample size.

Warning

This function is 'experimental' only, since it is not thoroughly tested yet. Especially for design="IBD" reliable test cases are missing.

Author(s)

D. Labes

References

Chow SC, Liu JP. *Design and Analysis of Bioavailability and Bioequivalence Studies.* Boca Raton: CRC Press; 3rd edition 2009.

Patterson S, Jones B. *Bioequivalence and Statistics in Clinical Pharmacology.* Boca Raton: Chapman & Hall/CRC: 2006. p. 239.
(contains presumably a bug)

Sethuraman VS, Leonov S, Squassante L, Mitchell TR, Hale MD. *Sample size calculation for the Power Model for dose proportionality studies.* Pharm Stat. 2007;6(1):35–41. doi:10.1002/pst.241

Hummel J, McKendrick S, Brindley C, French R. *Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion.* Pharm. Stat. 2009;8(1):38–49. doi:10.1002/pst.326

See Also

power.dp, bib.CL

Examples

```
# using all the defaults, i.e. crossover design, alpha=0.05
# theta1=0.8, theta2=1.25 but true slope slightly off 1
sampleN.dp(CV = 0.2, doses = c(1, 2, 8), beta0 = 1.02)
# should give n=18, power=0.854528


# incomplete block design with 5 doses, 3 periods
# from library(crossdes)
doses  <- c(5, 25, 50, 100, 200)
CVb    <- mse2CV(0.8)
levels <- length(doses)
per    <- 3
block  <- levels*(levels-1)/(per-1)
# IBD based on balanced minimal repeated measurements design
# gives n=30 and 10 sequences
ibd    <- crossdes::balmin.RMD(levels, block, per)
sampleN.dp(CV = 0.2, doses = doses, beta0 = 1, design = "IBD", dm = ibd,
          CVb = CVb, targetpower=0.9)
```

---

sampleN.HVNTID	*Sample size estimation for BE decision via FDA method for highly variable (HV) narrow therapeutic index drugs (NTIDs)*

Description

This function performs the sample size estimation for the BE decision via the FDA's method for highly variable NTIDs as described in respective guidances based on simulations.
The study designs may be the full replicate design 2x2x4 with 4 periods (TRTR|RTRT) and the 3-period replicate design 2x2x3 with sequences RTR|TRT.

Usage

```
sampleN.HVNTID(alpha = 0.05, targetpower = 0.8, theta0, theta1, theta2, CV,
               design = c("2x2x4", "2x2x3"), nsims = 1e+05, nstart, imax = 100,
               print = TRUE, details = TRUE, setseed = TRUE)
```

Arguments

alpha	Type I error probability. Per convention mostly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
theta0	'True' or assumed T/R ratio. Defaults to 0.95 if not given explicitly.
theta1	Conventional lower ABE limit to be applied in the FDA procedure. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the FDA procedure. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).

- If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR).
- If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].

design	Design of the study to be planned. "2x2x4" is the full replicate with 2 sequences and 4 periods (TRTR|RTRT). "2x2x3" is the full replicate with 2 sequences and 3 periods (TRT|RTR). Defaults to design="2x2x4".
nsims	Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+5.
nstart	Set this to a start value for the sample size if a previous run failed. May be missing.
imax	Maximum number of steps in sample size search. Defaults to 100.
print	If TRUE (default) the function prints its results. If FALSE only the resulting dataframe will be returned.
details	If set to TRUE, the default, the steps during sample size search are shown. Moreover the details of the method settings are printed.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power values for different runs a set.seed(123456) is issued if setseed=TRUE, the default.

Details

For deciding BE the study must pass the conventional ABE test and additionally the test that the ratio of sWT/sWR is <= 2.5.

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on these method.
Details can be found in a document `Implementation_scaledABE_sims` located in the `/doc` sub-directory of the package.

The estimated sample size gives always the *total* number of subjects (not subject/sequence – like in some other software packages).

Value

Returns a data.frame with the input and sample size results.
The `Sample` size column contains the total sample size.
The `nlast` column contains the last `n` value. May be useful for re-starting.

Warning

For some input constellations the sample size search may be very time consuming and will eventually also fail since the start values chosen may not really reasonable for them.
In case of a failed sample size search you may restart with setting the argument `nstart`.

Note

The design recommended by the FDA is the full replicate design `"2x2x4"`.
The sample size estimation is done only for balanced studies since the break down of the total subject number in case of unbalanced sequence groups is not unique. Moreover the formulas used are only valid for balanced designs.
The FDA method is described for the ABE limits 0.8 ... 1.25 only. Setting theta1, theta2 to other values may not be reasonable and is not tested.
The minimum sample size is 6, even if the power is higher than the intended targetpower.

The method is also required by China's Center of Drug Evaluation.

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Dabigatran Etexilate Mesylate.* Recommended Jun 2012; Revised Sep 2015, Jul 2017. download

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Rivaroxaban.* Recommended Sep 2015. download

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Edoxaban Tosylate.* Recommended May 2017; Revised Mar 2020. download

See Also

power.HVNTID
and power.NTIDFDA, sampleN.NTIDFDA for NTIDs with low variability

Examples

```
# using all defaults but CV
sampleN.HVNTID(CV = 0.3)
# should give
# n=22 with an (empirical) power of 0.829700

# Test formulation with lower variability but same pooled CV
CVs <- CVp2CV(0.3, ratio = 0.25)
sampleN.HVNTID(CV = CVs)
# should give (no distinct difference to example above)
# n=22 with an (empirical) power of 0.837520
```

---

sampleN.noninf	*Sample size for the non-inferiority t-test*

Description

Function for estimating the sample size needed to have a pre-specified power for the one-sided non-inferiority *t*-test for normal or log-normal distributed data.

Usage

```
sampleN.noninf(alpha = 0.025, targetpower = 0.8, logscale = TRUE,
               margin,theta0, CV, design = "2x2", robust = FALSE,
               details = FALSE, print = TRUE, imax=100)
```

Arguments

alpha	Significance level (one-sided). Defaults here to 0.025.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
logscale	Should the data used on log-transformed or on original scale? TRUE (default) or FALSE.
theta0	'True' or assumed T/R ratio or difference. In case of logscale=TRUE it must be given as ratio T/R. If logscale=FALSE, the difference in means. In this case, the difference may be expressed in two ways: relative to the same (underlying) reference mean, i.e. as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case the units of margin and CV need also be given relative to the reference mean (specified as ratio). Defaults to 0.95 if logscale=TRUE or to -0.05 if logscale=FALSE
margin	Non-inferiority margin. In case of logscale=TRUE it is given as ratio. If logscale=FALSE, the limit may be expressed in two ways: difference of means relative to the same (underlying) reference mean or in units of the difference of means. Note that in the former case the units of CV and theta0 need also be given relative to the reference mean (specified as ratio). Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.

CV	In case of `logscale=TRUE` the (geometric) coefficient of variation given as ratio. If `logscale=FALSE` the argument refers to (residual) standard deviation of the response. In this case, standard deviation may be expressed two ways: relative to a reference mean (specified as ratio sigma/muR), i.e. again as a coefficient of variation; or untransformed, i.e. as standard deviation of the response. Note that in the former case the units of `theta0`, `theta1` and `theta2` need also be given relative to the reference mean (specified as ratio).
	In case of cross-over studies this is the within-subject CV, in case of a parallel-group design the CV of the total variability.
design	Character string describing the study design. See [known.designs](#) for designs covered in this package.
robust	Defaults to FALSE. With that value the usual degrees of freedom will be used. Set to TRUE will use the degrees of freedom according to the 'robust' evaluation (aka Senn's basic estimator). These df are calculated as `n-seq`. See `known.designs()$df2` for designs covered in this package. Has only effect for higher-order crossover designs.
details	If TRUE the design characteristics and the steps during sample size calculations will be shown. Defaults to FALSE.
print	If TRUE (default) the function prints its results. If FALSE only the data.frame with the results will be returned.
imax	Maximum number of steps in sample size search. Defaults to 100. Adaption only in rare cases needed.

Details

The sample size is calculated via iterative evaluation of `power.noninf()`.
Start value for the sample size search is taken from a large sample approximation.
The sample size is bound to 4 as minimum.

The estimated sample size gives always the *total* number of subjects (not subject/sequence in crossovers or subjects/group in parallel designs – like in some other software packages).

Notes on the underlying hypotheses
If the supplied margin is < 0 (`logscale=FALSE`) or < 1 (`logscale=TRUE`), then it is assumed higher response values are better. The hypotheses are
H0: theta0 <= margin vs. H1: theta0 > margin,
where theta0 = mean(test)-mean(reference) if logscale=FALSE
or
H0: log(theta0) <= log(margin) vs. H1: log(theta0) > log(margin),
where theta0 = mean(test)/mean(reference) if logscale=TRUE.

If the supplied margin is > 0 (`logscale=FALSE`) or > 1 (`logscale=TRUE`), then it is assumed lower response values are better. The hypotheses are
H0: theta0 >= margin vs. H1: theta0 < margin

where theta0 = mean(test)-mean(reference) if logscale=FALSE
or
H0: log(theta0) >= log(margin) vs. H1: log(theta0) < log(margin)
where theta0 = mean(test)/mean(reference) if logscale=TRUE.
This latter case may also be considered as 'non-superiority'.

Value

A data.frame with the input settings and results will be returned.
Explore it with str(sampleN.noninf(...)

Warning

The function does not vectorize properly.
If you need sample sizes with varying CVs, use f.i. for-loops or the apply-family.

Author(s)

D. Labes

References

Julious SA. *Sample sizes for clinical trials with Normal data.* Stat Med. 2004;23(12):1921–86.
doi:10.1002/sim.1783

See Also

known.designs, power.noninf

Examples

```
# using all the defaults: margin=0.8, theta0=0.95, alpha=0.025
# log-transformed, design="2x2"
sampleN.noninf(CV = 0.3)
# should give n=48
#
# 'non-superiority' case, log-transformed data
# with assumed 'true' ratio somewhat above 1
sampleN.noninf(CV = 0.3, targetpower = 0.9,
               margin = 1.25, theta0 = 1.05)
# should give n=62
```

| sampleN.NTID | *Sample size estimation for BE decision via the FDA's method for narrow therapeutic index drugs (NTIDs)* |

Description

This function performs the sample size estimation for the BE decision for the FDA's method for NTIDs based on simulations. The study design is the full replicate design 2x2x4 (TRTR|RTRT) or the 3-period replicate design with sequences TRT|RTR.

Usage

```
sampleN.NTID(alpha = 0.05, targetpower = 0.8, theta0, theta1, theta2, CV,
             design = c("2x2x4", "2x2x3"), nsims = 1e+05, nstart, imax = 100,
             print = TRUE, details = TRUE, setseed = TRUE)
```

Arguments

alpha	Type I error probability. Per convention mostly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
theta0	'True' or assumed T/R ratio. Attention! Defaults here to 0.975 if not given explicitly. The value was chosen closer to 1 because the potency (contents) settings for NTIDs are tightened by the FDA.
theta1	Conventional lower ABE limit to be applied in the FDA procedure. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the FDA procedure. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). - If given as a scalar (length(CV) == 1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT == CVwR). - If given as a vector (length(CV) == 2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
design	Design of the study to be planned. "2x2x4" is the full replicate with 2 sequences and 4 periods (TRTR|RTRT). "2x2x3" is the full replicate with 2 sequences and 3 periods (TRT|RTR). Defaults to design = "2x2x4".
nsims	Number of simulations to be performed to obtain the empirical power. Defaults to 100,000 = 1e+5.
nstart	Set this to a start value for the sample size if a previous run failed. May be missing.
imax	Maximum number of steps in sample size search. Defaults to 100.

print   If `TRUE` (default) the function prints its results. If `FALSE` only the resulting
                        dataframe will be returned.

details   If set to `TRUE`, the default, the steps during sample size search are shown. More-
                        over the details of the method settings are printed.

setseed   Simulations are dependent on the starting point of the (pseudo) random number
                        generator. To avoid differences in power values for different runs a `set.seed(123456)`
                        is issued if `setseed = TRUE`, the default.

Details

The linearized scaled ABE criterion is calculated according to the SAS code given in the FDA's
guidances. For deciding BE the study must pass that criterion, the conventional ABE test, and that
the upper confidence limit of $\sigma_{\mathrm{wT}}/\sigma_{\mathrm{wR}} \leq 2.5$.

The simulations are done via the distributional properties of the statistical quantities necessary for
deciding BE based on this method.
Details can be found in a document `Implementation_scaledABE_sims` located in the `/doc` sub-
directory of the package.

The estimated sample size gives always the *total* number of subjects (not subject / sequence –
like in some other software packages).

Value

Returns a data frame with the input settings and sample size results.
The `Sample size` column contains the total sample size.
The `nlast` column contains the last `n` value. May be useful for re-starting.

Warning

For some input combinations the sample size search may be very time consuming and will eventu-
ally even fail since the start values chosen may not really reasonable for them. This applies espe-
cially for `theta0` values close to the implied scaled limits according to $\exp(\mp 1.053605 \times s_{\mathrm{wR}})$.
In case of a failed sample size search you may restart with setting the argument `nstart`.
In case of `theta0` values outside the implied scaled (tightened/widened) ABE limits no sample size
estimation is possible and the function throws an error (f.i. `CV = 0.04`, `theta0 = 0.95`).

Note

The design recommended by the FDA is the full replicate design `"2x2x4"`.
The sample size estimation is done only for balanced studies since the break down of the total sub-
ject number in case of unbalanced sequence groups is not unique. Moreover the formulas used are
only valid for balanced designs.
The FDA method is described for the ABE limits 0.8 ... 1.25 only. Setting `theta1`, `theta2` to other
values may not be reasonable and is not tested.
The results for the design `"2x2x3"` are to be considered as experimental since at present not thor-
ougly tested.
The minimum sample size is 6, even if the power is higher than the intended targetpower.

The method is also required by China's Center of Drug Evaluation.

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Warfarin Sodium.* Recommended Dec 2012. download

Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Draft Guidance for Industry. Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA.* August 2021. download

Yu LX, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann DJ, Muldowney L, Chen ML, Davit B, Conner D, Woodcock J. *Novel bioequivalence approach for narrow therapeutic index drugs.* Clin Pharmacol Ther. 2015;97(3):286–91. doi:10.1002/cpt.28

Jiang W, Makhlouf F, Schuirmann DJ, Zhang X, Zheng N, Conner D, Yu LX, Lionberger R. *A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion.* AAPS J. 2015;17(4):891–901. doi:10.1208/s1224801597535

Endrényi L, Tóthfalusi L. *Determination of Bioequivalence for Drugs with Narrow Therapeutic Index: Reduction of the Regulatory Burden.* J Pharm Pharm Sci. 2013;16(5):676–82. open access

See Also

power.NTID and power.HVNTID, sampleN.HVNTID for NTIDs with high variability

Examples

```
sampleN.NTID(CV = 0.04,theta0 = 0.975)
# should give
# n=54 with an (empirical) power of 0.809590
#
# Test formulation with lower variability
sampleN.NTID(CV = c(0.04,0.06),theta0 = 0.975)
# should give
# n=20 with an (empirical) power of 0.0.814610
#
# alternative 3-period design
sampleN.NTID(CV = 0.04,theta0 = 0.975, design="2x2x3")
# should give
# n=86 with power = 0.80364
```

---

sampleN.RatioF   *Sample size for equivalence of the ratio of two means with normality on original scale*

Description

Estimates the necessary sample size to have at least a given power based on Fieller's confidence ('fiducial') interval.

Usage

```
sampleN.RatioF(alpha = 0.025, targetpower = 0.8, theta1 = 0.8, theta2,
               theta0 = 0.95, CV, CVb, design = "2x2", print = TRUE,
               details = FALSE, imax=100, setseed=TRUE)
```

Arguments

alpha
: Type I error probability.
  Defaults here to 0.025 because this function is intended for studies with clinical endpoints.

targetpower
: Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.

theta1
: Lower bioequivalence limit. Typically 0.8 (default).

theta2
: Upper bioequivalence limit. Typically 1.25.
  Is set to 1/theta1 if missing.

theta0
: 'True' or assumed T/R ratio. Typically set to 0.95.

CV
: Coefficient of variation as ratio. In case of design="parallel" this is the CV of the total variability, in case of design="2x2" the intra-subject CV (CVw in the reference).

CVb
: CV of the between-subject variability. Only necessary for design="2x2".

design
: A character string describing the study design.
  design="parallel" or design="2x2" allowed for a two-parallel group design or a classical TR|RT crossover design.

print
: If TRUE (default) the function prints its results. If FALSE only a data.frame with the results will be returned.

details
: If TRUE the steps during sample size calculations will be shown.
  Defaults to FALSE.

imax
: Maximum number of steps in sample size search.
  Defaults to 100. Adaption only in rare cases needed.

setseed
: If set to TRUE the dependence of the power from the state of the random number generator is avoided.

Details

The sample size is based on exact power calculated using the bivariate non-central *t*-distribution via function [pmvt](#) of the package mvtnorm.
Due to the calculation method used in package mvtnorm these probabilities are dependent from the state of the random number generator within the precision of the power.

The CV(within) and CVb(etween) in case of design="2x2" are obtained via an appropriate ANOVA from the error term and from the difference (MS(subject within sequence)-MS(error))/2.

The estimated sample size gives always the *total* number of subjects (not subject/sequence in crossovers or subjects/group in parallel designs – like in some other software packages).

Value

A data.frame with the input values and results will be returned.
The sample size n returned is the total sample size for both designs.

Note

This function is intended for studies with clinical endpoints.
In such studies the 95% confidence intervals are usually used for equivalence testing.
Therefore, alpha defaults here to 0.025 (see EMEA 2000).

Author(s)

D. Labes

References

Fieller EC. *Some Problems in Interval Estimation.* J Royal Stat Soc B. 1954;16(2):175–85. [doi:10.1111/j.25176161.1954.tb00159.x](#)

Sasabuchi S. *A test of a multivariate normal mean with composite hypotheses determined by linear inequalities.* Biometrika. 1980;67(2):429–39. [doi:10.1093/biomet/67.2.429](#)

Hauschke D, Kieser M, Diletti E, Burke M. *Sample size determination for proving equivalence based on the ratio of two means for normally distributed data.* Stat Med. 1999;18(1):93–105.

Hauschke D, Steinijans V, Pigeot I. *Bioequivalence Studies in Drug Development.* Chichester: Wiley; 2007. Chapter 10.

European Agency for the Evaluation of Medicinal Products, CPMP. *Points to Consider on Switching between Superiority and Non-Inferiority.* London, 27 July 2000. [CPMP/EWP/482/99](#)

See Also

[power.RatioF](#)

Examples

```
# sample size for a 2x2 cross-over study
# with CVw=0.2, CVb=0.4
# alpha=0.025 (95% CIs), target power = 80%
# 'true' ratio = 95%, BE acceptance limits 80-125%
# using all the defaults:
sampleN.RatioF(CV = 0.2, CVb = 0.4)
# gives n=28 with an achieved power of 0.807774
# see Hauschke et.al. (2007) Table 10.3a

# sample size for a 2-group parallel study
# with CV=0.4 (total variability)
# alpha=0.025 (95% CIs), target power = 90%
# 'true' ratio = 90%, BE acceptance limits 75-133.33%
sampleN.RatioF(targetpower = 0.9, theta1 = 0.75,
               theta0 = 0.90, CV = 0.4, design = "parallel")
# gives n=236 with an achieved power of 0.900685
# see Hauschke et.al. (2007) Table 10.2

# a rather strange setting of ratio0! have a look at n.
# it would be better this is not the sample size but your account balance ;-).
sampleN.RatioF(theta0 = 0.801, CV = 0.2, CVb = 0.4)
```

---

sampleN.RSABE   *Sample size estimation for BE decision via linearized scaled ABE criterion*

Description

This function performs the sample size estimation for the BE decision via linearized scaled ABE criterion based on simulations.

Usage

```
sampleN.RSABE(alpha = 0.05, targetpower = 0.8, theta0, theta1, theta2, CV,
              design = c("2x3x3", "2x2x4", "2x2x3"), regulator = c("FDA", "EMA"),
               nsims = 1e+05, nstart, imax=100, print = TRUE,
               details = TRUE, setseed=TRUE)
```

Arguments

alpha	Type I error probability. Per convention mostly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.

theta1	Conventional lower ABE limit to be applied in the mixed procedure if `CVsWR <= CVswitch`.
	Also Lower limit for the point estimate constraint.
	Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if `CVsWR <= CVswitch`. Also upper limit for the point estimate constraint.
	Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).

- If given as a scalar (`length(CV)==1`) the *same* CV of Test and Reference is assumed (homoscedasticity, `CVwT==CVwR`).
- If given as a vector (`length(CV)==2`), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in `CV[1]` and the one of the Reference in the `CV[2]`.

design	Design of the study to be planned.
	`"2x3x3"` is the partial replicate design.
	`"2x2x4"` is a full replicate design with 2 sequences and 4 periods.
	`"2x2x3"` is a full replicate design with 2 sequences and 3 periods.
	Defaults to `design="2x3x3"`. Details are given the section about Designs.
regulator	Regulatory body settings for the scaled ABE criterion.
	Defaults to `design="FDA"`.
	Also the scaled ABE criterion is usually calculated with the FDA constant `r_const=log(1.25)/0.25` you can override this behavior to use the EMA setting `r_const=0.76` to avoid the discontinuity at CV=30% and be more stringent.
nsims	Number of simulations to be performed to obtain the (empirical) power.
nstart	Set this to a start for the sample size search if a previous run failed.
	After reworking the start n in version 1.1-05 rarely needed.
imax	Maximum number of steps in sample size search. Defaults to 100.
print	If `TRUE` (default) the function prints its results. If `FALSE` only the result data.frame will be returned.
details	If set to `TRUE`, the default, the steps during sample size search are shown.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a `set.seed(123456)` is issued if `setseed=TRUE`, the default.

Details

The linearized scaled ABE criterion is calculated according to the SAS code given in the FDA progesterone guidance.

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on scaled ABE.
For more details see a document `Implementation_scaledABE_simsVx.yy.pdf` in the /doc subdirectory of the package.

If a CVcap is defined for the regulator, the BE decision is based on the inclusion of the CI in

the capped widened acceptance limits in case of CVwR > CVcap. This resembles method 'Howe-EMA' in Muñoz *et al.* and is the standard behavior now if `regulator="EMA"` is choosen.

The estimated sample size gives always the *total* number of subjects (not subject/sequence – like in some other software packages).

Value

Returns a data.frame with the input and sample size results.
The Sample size column contains the total sample size.
The nlast column contains the last n value. May be useful for restarting.

Designs

Although some designs are more 'popular' than others, sample size estimations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

The sample size estimation for theta0 >1.2 and <0.85 may be very time consuming and will eventually also fail since the start values chosen are not really reasonable in that ranges. This is especially true in the range about CV = 0.3 and regulatory constant according to FDA.
If you really need sample sizes in that range be prepared to restart the sample size estimation via the argument nstart.
Since the dependence of power from n is very flat in the mentioned region you may also consider to adapt the number of simulations not to tap in the simulation error trap.

Note

The sample size estimation is done only for balanced designs since the break down of the total subject number in case of unbalanced sequence groups is not unique. Moreover the formulas used are only for balanced designs.
The minimum sample size is n=6, even if the power is higher than the intended targetpower.

Author(s)

D. Labes

References

Food and Drug Administration, Office of Generic Drugs (OGD). *Draft Guidance on Progesterone.* Recommended Apr 2010. Revised Feb 2011. download

Tóthfalusi, L, Endrényi, L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open access

Tóthfalusi L, Endrényi L, García Arieta A. *Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence.* Clin Pharmacokin. 2009;48(11):725–43. doi:10.2165/11318040-00000000000000

Muñoz J, Alcaide D, Ocaña J. *Consumer's risk in the EMA and FDA regulatory approaches for bioequivalence in highly variable drugs.* Stat Med. 2015;35(12):1933–43. doi:10.1002/sim.6834

See Also

power.RSABE, power.scABEL

Examples

```
# using all the defaults:
# design=2x3x3 (partial replicate design), theta0=0.90,
# ABE limits, PE constraint 0.8 - 1.25
# targetpower=80%, alpha=0.05, 1E5 simulations
sampleN.RSABE(CV = 0.3)
# should result in a sample size n=45, power=0.80344
```

---

sampleN.RSABE2L.sdsims

Sample size estimation for BE Decision via Reference Scaled ABE

Description

These functions performs the sample size estimation of the BE decision via the reference scaled ABE based on **subject data** simulations. Implemented are the methods ABEL, Hyslop and 'exact' (see the References in power.RSABE2L.sdsims).

The estimation method of the key statistics needed to perform the RSABE decision is the usual ANOVA.

This function has an alias sampleN.RSABE2L.sds().

Usage

```
sampleN.RSABE2L.sdsims(alpha = 0.05, targetpower = 0.8, theta0,
                       theta1, theta2, CV,
                       design = c("2x3x3", "2x2x4", "2x2x3"),
                       SABE_test = "exact", regulator, nsims=1e5,
                       nstart, imax = 100, print = TRUE,
                       details = TRUE, setseed = TRUE, progress)
```

Arguments

alpha	Type I error probability. Per convention mostly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also Lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). • If given as a scalar (length(CV)==1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR). • If given as a vector (length(CV)==2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
design	Design of the study to be planned. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods. "2x2x3" is a full replicate design with 2 sequences and 3 periods. Defaults to design="2x3x3". Details are given the section about Designs.
SABE_test	This argument specifies the test method to be used for the reference scaled ABE decision. Default is the "exact" 'ncTOST' method of the two Laszlós. Other choices are "ABEL", "Hyslop" and "FDA". See Details. This argument may be given also in lower case.
regulator	Regulatory settings for the widening of the BE acceptance limits. May be given as character "EMA" or as an object of class 'regSet' (see [reg_const](#)). Defaults to regulator="EMA" if missing. This argument may be given also in lower case if given as character. If given as object of class 'regSet' the component est_method can not be "ISC".
nsims	Number of simulations to be performed to obtain the (empirical) power. The default value 100,000 = 1e+5 is usually sufficient. Consider to rise this value if theta0<=0.85 or >=1.25. But see the warning section.
nstart	Set this to a start for the sample size search if a previous run failed. After reworking the start n in version 1.1-05 rarely needed.
imax	Maximum number of steps in sample size search. Defaults to 100.
print	If TRUE (default) the function prints its results. If FALSE only the result data.frame will be returned.
details	If set to TRUE (default), the steps during sample size search are shown.

setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(123456) is issued if setseed=TRUE, the default.
progress	Should a progressbar be shown? Defaults to TRUE if missing and nsims >5E5.

Details

The methods rely on the analysis of log-transformed data, *i.e.*, assume a log-normal distribution on the original scale.

The widened BE acceptance limits will be calculated by the formula
[L, U] = exp(± r_const * sWR)
with r_const the regulatory constant and sWR the standard deviation of the within subjects variability of the Reference. r_const = 0.76 (~log(1.25)/0.29356) is used in case of regulator="EMA". If the CVwR of the Reference is < CVswitch=0.3 the conventional ABE limits apply (mixed procedure).
In case of regulator="EMA" a cap is placed on the widened limits if CVwr>0.5, *i.e.*, the widened limits are held at value calculated for CVwR=0.5.

The simulations are done by simulating subject data (all effects fixed except the residuals) and evaluating these data via ANOVA of all data to get the point estimate of T vs. R along with its 90% CI and an ANOVA of the data under R(eference) only to get an estimate of s2wR.

The estimated sample size gives always the *total* number of subjects (not subject/sequence – like in some other software packages).

Value

Returns a data.frame with the input settings and sample size results.
The Sample size column contains the total sample size.
The nlast column contains the last n value. May be useful for restarting.

Designs

Although some designs are more 'popular' than others, sample size estimations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

The sample size estimation for very extreme theta0 (<0.83 or >1.21) may be very time consuming and will eventually also fail since the start values chosen are not really reasonable in that ranges.
If you really need sample sizes in that range be prepared to restart the sample size estimation via

the argument nstart.

Since the dependence of power from n is very flat in the mentioned region you may also consider to adapt the number of simulations not to tap in the simulation error trap.

Note

We are doing the sample size estimation only for balanced designs since the break down of the total subject number in case of unbalanced sequence groups is not unique. Moreover the formulas used are only for balanced designs.

The minimum sample size is 6, even if the power is higher than the intended targetpower.

Subject simulations are relatively slow. Thus be patient and go for a cup of coffee if you use this function with high sample sizes!

Author(s)

H. Schütz

See Also

power.RSABE2L.sdsims, sampleN.scABEL, reg_const

Examples

```
# using the defaults:
# partial replicate design, targetpower=80%,
# true assumed ratio = 0.90, 1E+5 simulated studies
# ABE limits, PE constraint 0.8 - 1.25
# EMA regulatory settings
# compare results

CV     <- 0.4
method <- c("exact", "abel", "hyslop", "fda")
res    <- data.frame(SABE_test = c("ncTOST", "ABEL",
                                    "Hyslop", "FDA"),
                  n = NA, power = NA)
for (i in 1:nrow(res)) {
  res[i, 2:3] <- sampleN.RSABE2L.sdsims(CV = CV,
                                        SABE_test = method[i],
                                        details = FALSE,
                                        print = FALSE)[8:9]
}
print(res, digits = 4, row.names = FALSE)
# should result in a sample size n=48 with all methods,
# power=0.8197 (ncTOST), 0.8411 (ABEL), 0.8089 (Hyslop), 0.8113 (FDA)
```

| sampleN.scABEL | *Sample size estimation for BE decision via scaled (expanded) BE acceptance limits* |

Description

This function performs the sample size estimation via power calculations of the BE decision via scaled (expanded) BE acceptance limits, based on simulations.

Usage

```
sampleN.scABEL(alpha = 0.05, targetpower = 0.8, theta0, theta1, theta2,
               CV, design = c("2x3x3", "2x2x4", "2x2x3"), regulator,
               nsims = 1e+05, nstart, imax = 100, print = TRUE,
               details = TRUE, setseed = TRUE)
```

Arguments

alpha	Type I error probability. Per convention mostly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also Lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent). • If given as a scalar (length(CV) == 1) the *same* CV of Test and Reference is assumed (homoscedasticity, $CV_{wT} = CV_{wR}$). • If given as a vector (length(CV) == 2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
design	Design of the study to be planned. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods. "2x2x3" is a full replicate design with 2 sequences and 3 periods. Defaults to design="2x3x3". Details are given the section about Designs.
regulator	Regulatory settings for the widening of the BE acceptance limits. May be given as character from the choices "EMA", "HC", "GCC", "FDA" or as an object of class 'regSet' (see reg_const).

| | Defaults to regulator="EMA" if missing.
| | This argument may be given also in lower case if given as character.

nsims	Number of simulations to be performed to obtain the (empirical) power. The default value 100,000 = 1e+5 is usually sufficient. Consider to rise this value if theta0 <=0.85 or >=1.20. But see the warning section.
nstart	Set this to a start for the sample size search if a previous run failed. After reworking the start n in version 1.1-05 rarely needed.
imax	Maximum number of steps in sample size search. Defaults to 100.
print	If TRUE (default) the function prints its results. If FALSE only the result data.frame will be returned.
details	If set to TRUE (default), the steps during sample size search are shown.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(123456) is issued if setseed = TRUE, the default.

Details

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on ABEL ('Average Bioequivalence with Expanded Limits'). For more details see a description in the /doc sub-directory of the package.

Function sampleN.scABEL() is based on power calculations via simulations using the distributional characteristics of the 'key' statistics obtained from the EMA recommended evaluation via ANOVA if regulator="EMA" or if the regulator component est_method is set to "ANOVA" if regulator is an object of class 'regSet'.
Otherwise, the simulations are based on the distributional characteristis of the 'key' statistics obtained from evaluation via intra-subject contrasts (ISC), as recommended by the FDA.

The estimated sample size gives always the *total* number of subjects (not subject/sequence – like in some other software packages).

Function sampleN.scABEL2() is solely based on power calculations via simulation using the distributional characteristics of the 'key' statistics obtained from evaluation via intra-subject contrasts (ISC). This function is deprecated.

Value

Returns a data.frame with the input settings and sample size results.
The Sample size column contains the total sample size.
The nlast column contains the last n value. May be useful for restarting.

Designs

Although some designs are more 'popular' than others, sample size estimations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

The sample size estimation for extreme theta0 (<0.83 or >1.21) may be very time consuming and will eventually also fail since the start values chosen are not really reasonable in that ranges. This is especially true in the range around CV = 0.3 and regulatory constant according to FDA.
If you really need sample sizes in that range be prepared to restart the sample size estimation via the argument nstart.
Since the dependence of power from n is very flat in the mentioned region you may also consider to adapt the number of simulations not to get caught in the simulation error trap.

If results of power.scABEL are expected to be inaccurate (partial replicate design with unbalanced sequences and/or heteroscedasticity in the case of $CV_{wT} > CV_{wR}$, subject data via sampleN.scABEL.sdsims should be simulated instead. Very time consuming (easily 100times slower)! Subject data simulations are only supported for regulator="EMA" and regulator="GCC".

Note

We are doing the sample size estimation only for balanced designs since the break down of the total subject number in case of unbalanced sequence groups is not unique. Moreover the formulas used are only for balanced designs.

In case of regulator="FDA" the sample size is only approximate since the BE decision method is not exactly what is expected by the FDA. But the two Lászlós state that the scABEL method should be 'operationally' equivalent to the FDA method. Thus the sample size should be comparable.
Consider in case of regulator="FDA" to use the function sampleN.RSABE() instead.

In case of regulator="HC" the underlying power is only approximative since the Health Canada recommends evaluation by a mixed model approach. But this could only implemented via subject data simulations which are very time consuming.

The minimum sample size is 6, even if the power is higher than the intended targetpower.

Author(s)

D. Labes

References

Tóthfalusi L, Endrényi L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open access

See Also

power.scABEL, sampleN.scABEL.sdsims, sampleN.RSABE, reg_const

Examples

```
# using all the defaults:
# partial replicate design, targetpower=80%,
# true assumed ratio = 0.90, 1E+5 simulated studies
# ABE limits, PE constraint 0.8 - 1.25
# EMA regulatory settings
sampleN.scABEL(CV = 0.3)
# should result in a sample size n=54, power=0.8159

# Now with former (inofficial) ANVISA settings, CVswitch=40%
# (since 2016 ANVISA uses the same settings as EMA)
reg      <- reg_const("USER", r_const = 0.76, CVswitch = 0.4, CVcap = 0.5)
reg$name <- "Old ANVISA"
sampleN.scABEL(CV = 0.3, regulator = reg)
# should result in a sample size n=60, power=0.8101

# For the full replicate design, target power = 90%
# true assumed ratio = 0.9, FDA regulatory settings
# sims based on evalaution via ISC
sampleN.scABEL(CV = 0.4, targetpower = 0.9, design = "2x2x4",
               regulator = "FDA")
# should result in a sample size n=32, power=0.9125

# Fixed wider limits (0.7500 - 1.3333) for the GCC
sampleN.scABEL(CV = 0.4, targetpower = 0.9, design = "2x2x4",
               regulator = "GCC")
# should result in a sample size n=40, power=0.9039
```

---

sampleN.scABEL.ad   *Sample size estimation for ABEL and iteratively adjusted alpha*

Description

This function performs a sample size estimation for the BE decision via Average Bioequivalenc
with Expanding Limits (ABEL) based on simulations. Simultaneously alpha is iteratively adjusted
in order to maintain the consumer risk at the nominal level.

Usage

```
sampleN.scABEL.ad(alpha = 0.05, targetpower = 0.8, theta0, theta1, theta2,
                  CV, design = c("2x3x3", "2x2x4", "2x2x3"), regulator,
                  nstart = NA, nsims = 1e+06, imax = 100, tol,
                  print = TRUE, details = FALSE, alpha.pre = 0.05,
                  setseed = TRUE, sdsims = FALSE, progress)
```

Arguments

alpha	Type I error (TIE) probability (nominal level of the test). Per convention commonly set to 0.05.
targetpower	Power to achieve at least. Must be >0 and <1. Typical values are 0.80 to 0.90 (*i.e.*, 80% to 90%). Defaults to 0.80 if not given explicitly.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVwR == CVswitch. Also lower limit for the point estimate constraint. Defaults to 0.80 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVwR == CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).

- If given as a scalar (length(CV) == 1) the *same CV* of Test and Reference is assumed (homoscedasticity: $CV_{wT} = CV_{wR}$).
- If given as a vector (length(CV) == 2) – assuming heteroscedasticity – the *CV* of Test **must** be given in the *first* element and the one of Reference in the *second*.

design	Design of the study to be planned. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods. "2x2x3" is a full replicate design with 2 sequences and 3 periods. Defaults to "2x3x3". Details are given the section about Designs.
regulator	Regulatory settings for the widening of the BE acceptance limits. Choose from "EMA" (default), "HC", or "GCC". This argument may be given also in lower case.
nstart	Best "guess" sample size. If not given (default), simulations start with the sample size estimated for alpha (or alpha.pre, if given), theta0, and targetpower. Can also be set to start the sample size search if a previous run failed. According to regulatory requirements must be >=12 for the EMA and >=24 for ANVISA.
nsims	Number of simulations to be performed to estimate the (empirical) TIE and in each iteration of adjusting alpha. The default value 1,000,000 = 1E+6 should not be lowered.
imax	Maximum number of steps in sample size search. Defaults to 100.
tol	Desired accuracy (convergence tolerance). Defaults to 1E-6.
print	If TRUE (default), the function sends its results to the console.
details	If TRUE (default), the steps during sample size search are shown. Additionally information about the impact on power by adjusting alpha and change of study costs due to the increased sample size is given.
alpha.pre	Pre-specified alpha (optional). Must be <=alpha. ABEL will be performed at level alpha.pre and the TIE assessed at level alpha. Less powerful than adjusting alpha but an alternative in the critical region of

maximum inflation of the TIE. In certain scenarios Bonferroni's 0.025 is not sufficient to preserve the Type I Error.

Not recommended if $CV_{wR} \geq 0.45$ due to poor power characteristics.

setseed   Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs set.seed(123456) is issued if setseed = TRUE (default).

sdsims   If FALSE (default) power is estimated by the respective 'key' statistics. Recommended for speed reasons.

Set to TRUE if results of power.scABEL are expected to be inaccurate (partial replicate design with unbalanced sequences and/or heteroscedasticity where $CV_{wT} > CV_{wR}$) and subject data via power.scABEL.sdsims should be simulated instead. Very time consuming (easily 100times slower)! Subject data simulations are only supported for regulator = "EMA" and regulator = "GCC".

progress   Set to TRUE if a progress bar should be displayed. Defaults to FALSE. Ignored if sdsims = FALSE.

Details

The simulations are done via the distributional properties of the statistical quantities necessary for assessing BE based on ABEL. Simulations of the TIE are performed at the upper (expanded) limit *U* of the acceptance range. Due to the symmetry around 1 results are valid for the lower (expanded) limit *L* as well.

U at the EMA's and Health Canada's CVcap, the GCC's for *any* $CV_{wR} > 0.30$:

```
scABEL(CV = 0.5, reg = "EMA")[["upper"]]
[1] 1.43191
scABEL(CV = 0.57382, reg = "HC")[["upper"]]
[1] 1.5
scABEL(CV = 0.31, reg = "GCC")[["upper"]]
[1] 1.333333
```

Simulated studies are evaluated by ANOVA (Method A) as recommended in the EMA's Q&A-document and by intra-subject contrasts if regulator="HC". Health Canada requires a mixed effects model which cannot be implemented in R. However, intra-subjects contrasts are a sufficiently close approximation.

If an inflation of the TIE is expected (*i.e.*, >alpha), alpha is iteratively adjusted until at least the target power is reached and the consumer risk is maintained (<=alpha). For details about the algorithm see the respective section of scABEL.ad.

The estimated sample size gives always the *total* number of subjects (not subject/sequence – like in some other software packages).

Value

Returns a data.frame with the input and results for adjusted alpha, type I error, sample size, and achieved power.

The Sample size column contains the total sample size. If no adjustment is necessary, NA will be returned in the alpha.adj column and other results are identical to the ones obtained by sampleN.scABEL.

Designs

Although some designs are more 'popular' than others, sample size estimations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

The sample size estimation for extreme theta0 (<0.83 or >1.21) may be time consuming and will eventually also fail since the start values chosen are not really reasonable in that ranges.
If you really need sample sizes in that range be prepared to restart the sample size estimation with nstart above the last one before failure.
Since the dependence of power from n is very flat in the mentioned region you may also consider to adapt the number of simulations not to tap in the simulation error trap.

See also the Warning section of the function power.scABEL concerning the power value agreement to those obtained from simulations via subject data.

For the GCC and $CV_{\mathrm{wR}} \leq 0.30$

Note

We are doing the sample size estimation only for balanced designs since the break down of the total subject number in case of unbalanced sequences is not unique. Moreover the formulas used are only for balanced designs.

Author(s)

H. Schütz

References

Tóthfalusi L, Endrényi L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open access

Wonnemann M, Frömke C, Koch A. *Inflation of the Type I Error: Investigations on Regulatory Recommendations for Bioequivalence of Highly Variable Drugs.* Pharm Res. 2015;32(1):135–43. doi:10.1007/s110950141450z

Muñoz J, Alcaide D, Ocaña J. *Consumer's risk in the EMA and FDA regulatory approaches for bioequivalence in highly variable drugs.* Stat Med. 2015;35(12):1933–43. doi:10.1002/sim.6834

Labes D, Schütz H. *Inflation of Type I Error in the Evaluation of Scaled Average Bioequivalence, and a Method for its Control.* Pharm Res. 2016;33(11):2805–14. doi:10.1007/s1109501620061

See Also

scABEL.ad, sampleN.scABEL, power.scABEL, scABEL

Examples

```
# --- Not run due to timing policy of CRAN for examples
# each may run some ten seconds or more
# using all the defaults:
# TRR|RTR|RRT, target power 80%, assumed ratio 0.90, 1E+6 simulated studies,
# EMA regulatory settings (ABE limits, PE constraint 0.8 - 1.25)

sampleN.scABEL.ad(CV = 0.3)
# should result in n 60, power 0.8022.
# Note: Without adjustment by sampleN.scABEL(): n 54, power 0.8159
# Easier to show the details:

sampleN.scABEL.ad(CV = 0.3, details = TRUE)
#
# TRTR|RTRT, target power 90%, pre-specified alpha 0.025

sampleN.scABEL.ad(CV = 0.3, targetpower = 0.9, design = "2x2x4", alpha.pre = 0.025)
# should result in n 60, power 0.9021; pre-specified alpha justified.
```

---

sampleN.scABEL.sdsims   *Sample size estimation for BE decision via scaled (expanded) BE acceptance limits*

Description

These functions performs the sample size estimation via power calculations of the BE decision via scaled (expanded) BE acceptance limits, based on **subject data** simulations.
This function has an alias sampleN.scABEL.sds().

Usage

```
sampleN.scABEL.sdsims(alpha = 0.05, targetpower = 0.8, theta0, theta1,
                      theta2, CV, design = c("2x3x3", "2x2x4", "2x2x3"),
                      regulator, nsims = 1e5, nstart, imax = 100,
                      print = TRUE, details = TRUE,
                      setseed = TRUE, progress)
```

Arguments

alpha   Type I error probability. Per convention mostly set to 0.05.

targetpower   Power to achieve at least. Must be >0 and <1.
               Typical values are 0.8 or 0.9.

theta0   'True' or assumed T/R ratio.
               Defaults to 0.90 according to the two Lászlós if not given explicitly.

theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also Lower limit for the point estimate constraint. Defaults to 0.8 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVsWR <= CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).

- If given as a scalar (length(CV) == 1) the *same CV* of Test and Reference is assumed (homoscedasticity, $CV_{wT} = CV_{wR}$).
- If given as a vector (length(CV) == 2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].

design	Design of the study to be planned. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods. "2x2x3" is a full replicate design with 2 sequences and 3 periods. Defaults to "2x3x3". Details are given the section about Designs.
regulator	Regulatory settings for the widening of the BE acceptance limits. May be given as "EMA", "GCC", or as an object of class 'regSet' (see [reg_const](#)). Defaults to regulator = "EMA" if missing. This argument may be given also in lower case if given as character. If given as object of class 'regSet' the component est_method must not be "ISC".
nsims	Number of simulations to be performed to obtain the (empirical) power. The default value 100,000 = 1e+5 is usually sufficient. Consider to rise this value if theta0 <=0.85 or >=1.20. But see the warning section.
nstart	Set this to a start for the sample size search if a previous run failed. After reworking the start n in version 1.1-05 rarely needed.
imax	Maximum number of steps in sample size search. Defaults to 100.
print	If TRUE (default) the function prints its results. If FALSE only the result data.frame will be returned.
details	If set to TRUE (default), the steps during sample size search are shown.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(123456) is issued if setseed = TRUE, the default.
progress	Should a progressbar be shown? Defaults to TRUE if missing and nsims >5E5.

Details

The methods rely on the analysis of log-transformed data, *i.e.*, assume a log-normal distribution on the original scale.

The expanded BE acceptance limits will be calculated by the formula
[L, U] = exp(± r_const * sWR)

with r_const the regulatory constant and sWR the standard deviation of the within subjects variability of the Reference. r_const = 0.76 (~log(1.25)/0.29356) is used in case of regulator = "EMA". If the CVwR is < CVswitch=0.3 the conventional ABE limits apply (mixed procedure).
In case of regulator="EMA" a cap is placed on the widened limits if $CV_{wR} > 0.50$, *i.e.*, the widened limits are held at value calculated for $CV_{wR} = 0.50$.
In case of regulator="GCC" *fixed* wider limits of 0.7500 – 1.3333 for $CV_{wR} > 0.30$ are applied and the conventional limits otherwise.

The simulations are done by simulating subject data (all effects fixed except the residuals) and evaluating these data via ANOVA of all data to get the point estimate of T vs. R along with its 90% CI and an ANOVA of the data under R(eference) only to get an estimate of s_{wR}^2.

The estimated sample size gives always the *total* number of subjects (not subject/sequence – like in some other software packages).

Value

Returns a data.frame with the input settings and sample size results.
The Sample size column contains the total sample size.
The nlast column contains the last n value. May be useful for restarting.

Designs

Although some designs are more 'popular' than others, sample size estimations are valid for *all* of the following designs:

"2x2x4"	TRTR	RTRT
	TRRT	RTTR
	TTRR	RRTT
"2x2x3"	TRT	RTR
	TRR	RTT
"2x3x3"	TRR	RTR	RRT

Warning

The sample size estimation for very extreme theta0 (<0.83 or >1.21) may be very time consuming and will eventually also fail since the start values chosen are not really reasonable in that ranges.
If you really need sample sizes in that range be prepared to restart the sample size estimation via the argument nstart.
Since the dependence of power from n is very flat in the mentioned region you may also consider to adapt the number of simulations not to get caught in the simulation error trap.

Note

We are doing the sample size estimation only for balanced designs since the break down of the total subject number in case of unbalanced sequence groups is not unique. Moreover the formulas used are only for balanced designs.
The minimum sample size is 6, even if the power is higher than the intended targetpower.

Subject simulations are easily more than 100times slower than simulations based on the 'key' statistics. We recommend this function only for the partial replicate design (TRR|RTR|RRT) assuming heteroscedasticity in the case of $CV_{wT} > CV_{wR}$.

Thus be patient and go for a cup of coffee if you use this function with high sample sizes!

Author(s)

H. Schütz

References

Tóthfalusi L, Endrényi L. *Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs.* J Pharm Pharmaceut Sci. 2011;15(1):73–84. open access

See Also

power.scABEL.sdsims, sampleN.scABEL, reg_const

Examples

```
# using the defaults:
# partial replicate design, targetpower=80%,
# true assumed ratio = 0.90, 1E+5 simulated studies
# ABE limits, PE constraint 0.8 - 1.25
# EMA regulatory settings
# Heteroscedasticity (CVwT 0.4, CVwR 0.3)
# compare results and run times

CV           <- c(0.4, 0.3)
expl         <- data.frame(method = c("subject simulations", "\'key\' statistics"),
                           n = NA, power = NA, seconds = NA)
start        <- proc.time()[[3]]
expl[1, 2:3] <- sampleN.scABEL.sdsims(CV = CV, print = FALSE,
                                      details = FALSE)[8:9]
expl[1, 4]   <- proc.time()[[3]] - start
start        <- proc.time()[[3]]
expl[2, 2:3] <- sampleN.scABEL(CV = CV, print = FALSE,
                               details = FALSE)[8:9]
expl[2, 4]   <- proc.time()[[3]] - start
print(expl, row.names = FALSE)
# should result in a sample size n=69, power=0.80198 for
# the subject simulations and n=66, power=0.80775 for the
# 'key' statistics
```

---

sampleN.TOST   *Sample size based on power of TOST*

Description

Estimates the necessary sample size to obtain at least a target (desired) power.

Usage

```
sampleN.TOST(alpha = 0.05, targetpower = 0.8, logscale = TRUE,
             theta0, theta1, theta2, CV, design = "2x2",
             method = "exact", robust = FALSE, print = TRUE,
             details = FALSE, imax=100)
```

Arguments

alpha   Significance level (one-sided). Commonly set to 0.05.

targetpower   Power to achieve at least. Must be >0 and <1.
                 Typical values are 0.8 or 0.9.

logscale   Should the data used on log-transformed (TRUE) or on original scale (FALSE)?
                 Defaults to TRUE.

theta0   'True' or assumed T/R ratio or difference.
                 In case of logscale = TRUE it must be given as ratio T/R.
                 If logscale = FALSE, the difference in means. In this case, the difference may
                 be expressed in two ways: relative to the same (underlying) reference mean, *i.e.*,
                 as (T-R)/R = T/R - 1; or as difference in means T-R. Note that in the former case
                 the units of CV, theta1 and theta2 need also be given relative to the reference
                 mean (specified as ratio).
                 Defaults to 0.95 if logscale = TRUE or to 0.05 if logscale = FALSE

theta1   Lower (bio-)equivalence limit.
                 In case of logscale = TRUE it is given as ratio.
                 If logscale = FALSE, the limit may be expressed in two ways: difference of
                 means relative to the same (underlying) reference mean or in units of the differ-
                 ence of means. Note that in the former case the units of CV, theta0 and theta2
                 need also be given relative to the reference mean (specified as ratio).
                 Defaults to 0.8 if logscale = TRUE or to -0.2 if logscale = FALSE.

theta2   Upper (bio-)equivalence limit.
                 In case of logscale = TRUE it is given as ratio. If logscale = FALSE, the limit
                 may be expressed in two ways: difference of means relative to the same (under-
                 lying) reference mean or in units of the difference of means. Note that in the
                 former case the units of CV, theta0 and theta1 need also be given relative to
                 the reference mean (specified as ratio).
                 If not given, theta2 will be calculated as 1/theta1 if logscale = TRUE or as
                 -theta1 if logscale = FALSE.

CV   In case of logscale=TRUE the (geometric) coefficient of variation given as ratio.
                 If logscale=FALSE the argument refers to (residual) standard deviation of the
                 response. In this case, standard deviation may be expressed two ways: relative
                 to a reference mean (specified as ratio sigma/muR), *i.e.*, again as a coefficient
                 of variation; or untransformed, *i.e.*, as standard deviation of the response. Note
                 that in the former case the units of theta0, theta1 and theta2 need also be
                 given relative to the reference mean (specified as ratio).

                 In case of cross-over studies this is the within-subject CV, in case of a parallel-
                 group design the CV of the total variability.

design   Character string describing the study design.
                See known.designs() for designs covered in this package.

method   Method for calculation of the power.
                Defaults to "exact" in which case the calculation is done based on formulas
                with Owen's Q. The calculation via Owen's Q can also be choosen with method
                = "owenq".
                Another exact method via direct use of the bivariate non-central *t*-distribution
                may be chosen with method = "mvt". This may have somewhat lower preci-
                sion compared to Owen's Q and has a much longer run-time.
                Approximate calculations can be choosen via method = "noncentral" or
                method = "nct" for the approximation using the non-central *t*-distribution.
                With method = "central" or method = "shifted" the relatively crude ap-
                proximation via the 'shifted' central *t*-distribution is chosen.
                The strings for method may be abbreviated.

robust   Defaults to FALSE. With that value the usual degrees of freedom will be used.
                Set to TRUE will use the degrees of freedom according to the 'robust' evaluation
                (aka Senn's basic estimator). These df are calculated as n-seq.
                See known.designs()$df2 for designs covered in this package.
                Has only effect for higher-order crossover designs.

print   If TRUE (default) the function prints its results. If FALSE only the data frame with
                the results will be returned.

details   If TRUE the design characteristics and the steps during sample size calculations
                will be shown. Defaults to FALSE.

imax   Maximum number of steps in sample size search.
                Defaults to 100. Adaption only in rare cases needed.

Details

The sample size is estimated via iterative evaluation of power of the TOST procedure.
Start value for the sample size search is taken from a large sample approximation according to
Zhang, modified.
The sample size is bound to 4 as minimum.

The estimated sample size gives always the *total* number of subjects (not subject/sequence in
crossovers or subjects/group in parallel designs – like in some other software packages).

Value

A data frame with the input and results will be returned.
The Sample size column contains the total sample size.

Warning

The function does not vectorize properly.
If you need sample sizes with varying CVs, use f.i. for-loops or the apply-family.

Note

Of course it is highly recommended to use the default method = "exact". :-)
There is no reason besides testing and for comparative purposes to use an approximation if the exact method is available at no extra costs.

Author(s)

D. Labes

References

Phillips KF. *Power of the Two One-Sided Tests Procedure in Bioequivalence.* J Pharmacokin Biopharm. 1990;18:137–44. doi:10.1007/BF01063556

Diletti D, Hauschke D, Steinijans VW. *Sample Size Determination for Bioequivalence Assessment by Means of Confidence Intervals.* Int J Clin Pharmacol Ther Toxicol. 1991;29(1):1–8.

Diletti D, Hauschke D, Steinijans VW. *Sample size determination: Extended tables for the multiplicative model and bioequivalence ranges of 0.9 to 1.11 and 0.7 to 1.43.* Int J Clin Pharmacol Ther Toxicol. 1992;30(Suppl 1):S59–62.

Zhang P. *A Simple Formula for Sample Size Calculation in Equivalence Studies.* J Biopharm Stat. 2003;13(3):529–38. doi:10.1081/BIP120022772

See Also

power.TOST, known.designs

Examples

```
# Exact calculation for a classical 2x2 cross-over (TR/RT),
# BE limits 80 ... 125%, assumed true BE ratio 0.95, intra-subject CV=30%,
# using all the default values
# should give n=40 power=0.815845
sampleN.TOST(CV = 0.3)

# Exact calculation for a parallel group design
# evaluation on the original (untransformed) scale
# BE limits 80 ... 120% = -20% ... +20% of reference,
# assumed true BE ratio 0.95% = -5% to reference mean,
# total CV=20%
# should give n=48 (total) power=0.815435
sampleN.TOST(logscale = FALSE, theta1 = -0.2, theta0 = -0.05,
             CV = 0.2, design = "parallel")

# A rather strange setting of theta0! Have a look at n.
# It would be better this is not the sample size but the running total
# of my bank account. But the first million is the hardest. ;-)
sampleN.TOST(CV = 0.2, theta0 = 0.8005)
```

Description

The (widened) scaled BE acceptance limits are calculated according to the regulatory settings of EMA, HC, FDA or via user defined regulatory settings.

Usage

```
scABEL(CV, regulator)
```

Arguments

CV   Coefficient of variation (of the Reference) as ratio.

regulator   Regulatory body settings for the widening of the BE acceptance limits.
                    May be given as character from the choices "EMA", "HC" (Health Canada),
                    "GCC" (Gulf Cooperation Council), "FDA" or as an object of class 'regSet' (see
                    reg_const).
                    Defaults to regulator="EMA" if missing.
                    The former regulator="ANVISA" is no longer allowed. The ANVISA recom-
                    mends since 2016 the EMA's regulatory settings.
                    The former regulator="USER" is no longer accepted but can be handled now
                    via function reg_const() to define an object with class 'regSet'.

Details

The widened BE acceptance limits are calculated by the formula
[L, U] = exp(-/+ r_const * sWR)
with r_const the regulatory constant and sWR the standard deviation of the within subjects variabil-
ity of the Reference.

- regulator="EMA" or regulator="HC"
  r_const = 0.76 (~ log(1.25)/sqrt(log(0.30^2+1)))
- regulator="GCC"
  r_const = 0.97997... (= log(1/0.75)/sqrt(log(0.30^2+1)))
- regulator="FDA"
  r_const = 0.89257... (= log(1.25)/0.25)

If the CVwR of the Reference is < CVswitch=0.3 the conventional ABE limits apply (mixed proce-
dure).

In case of regulator="EMA" a cap is placed on the widened limits if CVwR>0.5, *i.e.*, the widened
limits are held at the value calculated for CVwR=0.5.
In case of regulator="HC" the capping is done such that the acceptance limits are 0.6666 . . . 1.5 at
maximum, *i.e.*, CVcap=0.57382. Literally it is given by Health Canada rounded to three significant
digits as 57.4%.

Value

Returns a vector of lenghth 2 if one CV is given or a matrix if CV is given as vector with named components lower and upper of the scaled acceptance limits.

Note

The scaled acceptance limits (coined *'implied limits'* by Davit *et al.*) are not directly used in the BE evaluation for HVDP(s) recommended by the FDA. They are included here for comparative purposes. Moreover, there are controversies where to locate the *'implied limits'* and whether the so-called 'desired consumer-risk model' should be used.

Author(s)

D. Labes

References

Davit BM, Chen ML, Conner DP, Haidar SH, Kim S, Lee CH, Lionberger RA, Makhlouf FT, Nwakama PE, Patel DT, Schuirmann DJ, Yu LX. *Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration.* AAPS J. 2012;14(4):915–24. doi:10.1208/s122480129406x

Health Canada, Therapeutic Products Directorate. *Guidance Document. Comparative Bioavailability Standards: Formulations Used for Systemic Effects.* 2018/06/08. ISBN: 978-0-660-25514-9

See Also

power.scABEL, sampleN.scABEL, reg_const

Examples

```
scABEL(CV = 0.3, regulator = "EMA")
# should give the conventional (unscaled) BE limits:
# lower upper
#  0.80  1.25

scABEL(CV = 0.5, regulator = "EMA")
# should give the (maximum) expanded limits:
#     lower      upper
# 0.6983678 1.4319102

# define old ANVISA settings via reg_const()
rc       <- reg_const("USER", r_const = 0.76,
                      CVswitch = 0.4, CVcap = 0.5)
rc$name <- "ANVISAold"
scABEL(CV = 0.4, regulator = rc)
# should give the conventional (not expanded) limits:
# lower upper
#  0.80  1.25

scABEL(CV = 0.55, regulator = "HC")
```

```
# should give the widened limits:
#     lower     upper
# 0.6765789 1.4780241

scABEL(CV = 0.55, regulator = "GCC")
# should give the widened limits:
#    lower    upper
# 0.750000 1.333333

scABEL(CV = 0.55, regulator = "FDA")
# should give the 'implied' limits:
#     lower     upper
# 0.6320032 1.5822705
```

---

scABEL.ad   *Iteratively adjusted alpha for ABEL*

Description

This function iteratively adjusts alpha for the BE decision via Average Bioequivalence with Expanding Limits (ABEL) based on simulations in order to maintain the consumer risk at the nominal level.

Usage

```
scABEL.ad(alpha = 0.05, theta0, theta1, theta2, CV,
          design = c("2x3x3", "2x2x4", "2x2x3"), regulator,
          n, alpha.pre = 0.05, imax = 100, tol, print = TRUE,
          details = FALSE, setseed = TRUE, nsims = 1e+06,
          sdsims = FALSE, progress)
```

Arguments

alpha	Type I Error (TIE) probability (nominal level of the test). Per convention commonly set to 0.05.
theta0	'True' or assumed T/R ratio. Defaults to 0.90 according to the two Lászlós if not given explicitly.
theta1	Conventional lower ABE limit to be applied in the mixed procedure if CVwR == CVswitch. Also lower limit for the point estimate constraint. Defaults to 0.80 if not given explicitly.
theta2	Conventional upper ABE limit to be applied in the mixed procedure if CVwR == CVswitch. Also upper limit for the point estimate constraint. Defaults to 1.25 if not given explicitly.
CV	Intra-subject coefficient(s) of variation as ratio (not percent).
	• If given as a scalar (length(CV) == 1) the *same* CV of Test and Reference is assumed (homoscedasticity, CVwT==CVwR).

	• If given as a vector (length(CV) == 2), *i.e.*, assuming heteroscedasticity, the CV of the Test **must** be given in CV[1] and the one of the Reference in the CV[2].
design	Design of the study. "2x3x3" is the partial replicate design. "2x2x4" is a full replicate design with 2 sequences and 4 periods. "2x2x3" is a full replicate design with 2 sequences and 3 periods. Defaults to "2x3x3". Details are given the section about Designs.
regulator	Regulatory settings for the expanding of the BE acceptance limits. Choose from "EMA" (default), "HC", "GCC", or "FDA". This argument may also be given in lower case.
n	Total sample size of the study or a vector of sample size / sequences. If n leads to an unbalanced design (*i.e.*, is not a multiple of two in the full replicate designs or not a multiple of three in the partial replicate), the code tries to keep subjects / sequence as balanced as possible. In evaluating a particular *unbalanced* study **always** give n as a vector. Only if design = "2x2x3" (TRT|RTR) the *order* of sample sizes is important. n[1] is for sequence TRT and n[2] for sequence RTR. If n is missing, a sample size is estimated with target power 0.80 and pre-specified alpha if defined. Otherwise, alpha is used.
alpha.pre	Pre-specified alpha (optional). Must be <=alpha. ABEL will be performed at level alpha.pre and the TIE assessed at level alpha. Less powerful than adjusting alpha but an alternative in the critical region of maximum inflation of the TIE. In certain scenarios Bonferroni's 0.025 is not sufficient to preserve the Type I Error (*e.g.*, the third example). Not recommended if CVwR >= 0.45 due to poor power characteristics.
imax	Maximum number of steps in sample size search. Defaults to 100.
tol	Desired accuracy (convergence tolerance). Defaults to 1E-6.
print	If TRUE (default), the function sends its results to the console.
details	If TRUE, the *relative* change of the consumer risk in percent is shown. Additionally information about the impact on power (for specified theta0 and target power 0.80), runtime, and number of simulations (iterations) are given. Defaults to FALSE.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs set.seed(123456) is issued if setseed=TRUE (default).
nsims	Number of simulations to be performed to estimate the (empirical) TIE error and in each iteration of adjusting alpha. The default value 1,000,000 = 1E+6 should not be lowered.
sdsims	If FALSE (default) power is estimated by the respective 'key' statistics. Recommended for speed reasons. Set to TRUE if results of power.scABEL are expected to be inaccurate (partial replicate design with unbalanced sequences and/or heteroscedasticity where CVwT > CVwR) and subject data via power.scABEL.sdsims should be simulated instead. Very time consuming (easily 100times slower)! Subject data simulations are only supported for regulator = "EMA" and regulator = "GCC".

progress   Set to TRUE if a progress bar should be displayed. Ignored if sdsims = FALSE.

Details

The simulations are done via the distributional properties of the statistical quantities necessary for assessing BE based on ABEL. Simulations for the TIE are performed at the upper (expanded) limit *U* of the acceptance range. Due to the symmetry around 1 results are valid for the lower (expanded) limit *L* as well.
U at the EMA's and Health Canada's CVcap, the GCC's for *any* CVwR > 0.3:

```
scABEL(CV = 0.5, reg = "EMA")[["upper"]]
[1] 1.43191
scABEL(CV = 0.57382, reg = "HC")[["upper"]]
[1] 1.5
scABEL(CV = 0.5, reg = "GCC")[["upper"]]
[1] 1.333333
```

Simulated studies are evaluated by ANOVA (Method A) as recommended in the EMA' Q&A-document and by intra-subject contrasts if regulator = "HC". Health Canada requires a mixed-effects model which cannot be implemented in R. However, intra-subjects contrasts are a sufficiently close approximation.
The Type I Error in ABEL depends only on CVwR and – to a minor degree – the sample size. Algorithm:

1. The TIE is assessed based on alpha (or alpha.pre) and compared to the nominal level of the test alpha.

2. If no inflation of the TIE is found, the algorithm stops.

3. Otherwise, alpha is iteratively adjusted (*i.e.*, alpha.adj <alpha) until no more relevant inflation of the TIE is detected (*i.e.*, abs(TIE - alpha) <= tol).

Value

Sends results to the console if argument print=TRUE (default).
Returns a list with the input, adjusted alpha, and Type I Error (for nominal and adjusted alpha) if argument print=FALSE.
If no adjustment is necessary, NAs will be returned for the respective variables (alpha.adj, TIE.adj, rel.change, pwr.adj, rel.loss).

Designs

Although some designs are more 'popular' than others, power calculations are valid for *all* of the following designs:

"2x2x4"	TRTR | RTRT
	TRRT | RTTR
	TTRR | RRTT
"2x2x3"	TRT | RTR
	TRR | RTT
"2x3x3"	TRR | RTR | RRT

Warning

See the Warning section of the function `power.scABEL` concerning the power value agreement to
the one obtained by simulations via subject data.

Note

Specifying theta0 is not necessary.
If theta0 *is not* given, achievable power for the common target of 0.80 (both for alpha and adjusted
alpha) will be estimated. If theta0 *is* specified, its value will be used; again for target power 0.80.
If you are interested in other levels of power, use `sampleN.scABEL.ad`.

The EMA's method is currently recommended in other jurisdictions as well (*e.g.*, by the WHO; in
ASEAN States, Australia, Brazil, Egypt, the Eurasian Economic Union, New Zealand, and the East
African Community).
If CVwR > 30%, *fixed* wider limits of 0.7500–1.3333 are recommended by the Gulf Cooperation
Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates).

Author(s)

H. Schütz

References

Wonnemann M, Frömke C, Koch A. *Inflation of the Type I Error: Investigations on Regulatory
Recommendations for Bioequivalence of Highly Variable Drugs.* Pharm Res. 2015;32(1):135–43.
doi:10.1007/s110950141450z

Muñoz J, Alcaide D, Ocaña J. *Consumer's risk in the EMA and FDA regulatory approaches for
bioequivalence in highly variable drugs.* Stat Med. 2015;35(12):1933–43. doi:10.1002/sim.6834

Labes D, Schütz H. *Inflation of Type I Error in the Evaluation of Scaled Average Bioequivalence,
and a Method for its Control.* Pharm Res. 2016;33(11):2805–14. doi:10.1007/s1109501620061

Tóthfalusi L, Endrényi L. *Algorithms for Evaluating Reference Scaled Average Bioequivalence:
Power, Bias, and Consumer Risk.* Stat Med. 2017;36(27):4378–90. doi:10.1002/sim.7440

Molins E, Cobo E, Ocaña J. *Two-Stage Designs Versus European Scaled Average Designs in Bioe-
quivalence Studies for Highly Variable Drugs: Which to Choose?* Stat Med. 2017;36(30):4777–88.
doi:10.1002/sim.7452

European Medicines Agency, Committee for Medicinal Products for Human Use. *Guideline on the
Investigation of Bioequivalence.* London, 20 January 2010. CPMP/EWP/QWP/1401/98 Rev. 1/
Corr **

European Medicines Agency, Committee for Medicinal Products for Human Use. *Questions & An-
swers: positions on specific questions addressed to the Pharmacokinetics Working Party (PKWP).*
London, 19 November 2015. EMA/618604/2008 Rev. 13

Health Canada, Therapeutic Products Directorate. *Comparative Bioavailability Standards: For-
mulations Used for Systemic Effects, 2.1.1.8 Highly variable drug products* Ottawa, 08 June 2018.
online

Executive Board of the Health Ministers' Council for GCC States. *The GCC Guidelines for Bioe-
quivalence.* May 2021. Version 3.0 Saudi Food & Drug Authority *The GCC Guidelines for Bioe-
quivalence.* Version 3.1

See Also

sampleN.scABEL.ad, power.scABEL, power.scABEL.sdsims, scABEL

Examples

```
# Using all defaults:
# TRR|RTR|RRT, target power 80% for assumed ratio 0.90 (estimated sample size 54),
# EMA regulatory settings (ABE limits and PE constraint 0.80 - 1.25),
# 1E+6 simulated studies.
# Not run: due to timing policy of CRAN for examples

scABEL.ad(CV = 0.3)
# Should result in adjusted alpha 0.03389 (TIE 0.5000, TIE for nominal alpha 0.07189).
#
# As above but subject data simulations.

scABEL.ad(CV = 0.3, sdsims = TRUE)
# Should result in adjusted alpha 0.03336 (TIE 0.5000, TIE for nominal alpha 0.07237).
#
# TRT|RTR, heteroscedasticity, sample size 48 (unbalanced), subject data simulations.

scABEL.ad(CV = c(0.25, 0.3), design = "2x2x3", n = c(23, 25), sdsims = TRUE)
# Should result in adjusted alpha 0.02465 (TIE 0.5000, TIE for nominal alpha 0.09050).
#
# TRTR|RTRT, CV 0.35, sample size 33 (unbalanced).

scABEL.ad(CV = 0.35, design = "2x2x4", n = c(16, 17))
# Should result in adjusted alpha 0.03632 (TIE 0.5000, TIE for nominal alpha 0.06544).
```

---

type1error.2TOST   *Type I error rate for two simultaneous TOST procedures*

Description

Was designed to calculate the type I error rate of two simultaneous TOST procedures (where the two parameters of the two TOSTs are correlated with some correlation) for various study designs used in BE studies.

Is defunct now since it suffers from insufficient precision to obtain the type 1 error (TIE) via simulations.
Due to the intersection-union principle the TIE is always upper bounded to alpha by theory.

Index