Package ‘PowerTOST’

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Type Package

Title Power and Sample Size Based on Two One-Sided t-Tests (TOST) for (Bio)Equivalence Studies

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Description Contains functions to calculate power and sample size for various study designs used for bioequivalence studies. See function known.designs() for study designs covered. Moreover the package contains functions for power and sample size based on 'expected' power in case of uncertain (estimated) variability.

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Added are functions for the power and sample size for the ratio of two means with normally distributed data on the original scale (based on Fieller's confidence ('fiducial') interval).

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Contains further functions for power and sample size calculations based on non-inferiority t-test. This is not a TOST procedure but eventually useful if the question of 'non-superiority' must be evaluated. The power and sample size calculations based on non-inferiority test may also performed via 'expected' power in case of uncertain (estimated) variability.

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Contains functions power.scABEL() and sampleN.scABEL() to calculate power and sample size for the BE decision via scaled (widened) BE acceptance limits (EMA recommended) based on simulations. Contains also functions scABEL.ad() and sampleN.scABEL.ad() to iteratively adjust alpha in order to maintain the consumer risk in ABEL studies and adapt the sample size for the loss in power. Contains further functions power.RSABE() and sampleN.RSABE() to calculate power and sample size for the BE decision via reference scaled ABE criterion according to the FDA procedure based on simulations. Contains further functions power.NTIDFDA() and sampleN.NTIDFDA() to calculate power and sample size for the BE decision via the FDA procedure for NTID's based on simulations.
Contains further functions `power.HVNTID()` and `sampleN.HVNTID()` to calculate power and sample size for the BE decision via the FDA procedure for highly variable NTID's (see FDA Dabigatran / rivaroxaban guidances)

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Contains functions for power analysis of a sample size plan for ABE (pa.ABE()), scaled ABE (pa.scABE()) and scaled ABE for NTID's (pa.NTIDFDA()) analysing power if deviating from assumptions of the plan.

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Contains further functions for power calculations / sample size estimation for dose proportionality studies using the Power model.

**Imports** `mvtnorm, stats, utils, graphics, grDevices`

**Suggests** `crossdes`

**ByteCompile** yes

**License** GPL (>= 2)

**LazyLoad** yes

**LazyData** yes

**NeedsCompilation** no

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**Repository** CRAN

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Design matrices of period balanced incomplete block designs

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

Usage

bib.CL(trt, p)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>trt</td>
<td>Number of treatments (3 to 5).</td>
</tr>
<tr>
<td>p</td>
<td>Number of periods (2 to trt-1).</td>
</tr>
</tbody>
</table>
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, Liu
"Design and Analysis of Bioavailability and Bioequivalence Studies"
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 estimator, CV and n

Description
Utility function to calculate the 1-2*alpha CI's given point est., 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 estimator (GMR).
CV         Coefficient of variation of error variability as ratio.
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 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.

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-transformation.
The function assumes equal variances in case of design="parallel" and the higher order crossover designs.
The formula implemented covers balanced and unbalanced designs.

If 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 with number of subjects in sequence groups
CI.BE(pe=0.95, CV=0.3, n=c(12, 12))

---

CI.RatioF 1-2*alpha Fieller confidence interval given point est., CV (CVb) and n

Description

Utility function to calculate the 1-2*alpha Fieller CI’s given point est., CV (, CVb) and n for the parallel group and 2x2 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 estimator (ratio T/R).

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.

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 two-parallel group design or a classical TR/RT crossover design.

Details

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.

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 that case a warning is issued.

If 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.

Author(s)

D. Labes

References

Locke C.S.
"An exact confidence interval from untransformed data for the ratio of two formulation means."
ct5.1+ct5.2+ct5.3+ct5.4.1

Hauschke D., Steinijans V. and Pigeot I.
"Bioequivalence Studies in Drug Development"

See Also

CI.BE, power.RatioF

Examples

# 95% Fieller CI for the 2x2 crossover
CI.RatioF(pe=1.85, CV=0.3, CVB=0.6, n=24)

Sample size tables for the classical 2x2 crossover

Description

These data.frames give sample size tables calculated with sampleN.TOST() for the 2x2 design.

Details

The data.frame’s can be accessed by their names or by data("name").

ct5.1 is Table 5.1 from
Hauschke D., Steinijans V. and Pigeot I.
"Bioequivalence studies in Drug Development"
John Wiley & Sons, Chichester (2007)
Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1), exact

t5.2 is Table 5.2 from the same source
Multiplicative model, theta1=0.75, theta2=1.3333 (1/theta1), exact

t5.3 is Table 5.3 from the same source
Multiplicative model, theta1=0.9, theta2=1.1111 (1/theta1), exact

t5.4.1 is Table 5.4.1 from
Chow S.C., Liu J.P.
"Design and Analysis of Bioavailability and Bioequivalence Studies"
Additive model, theta1=-0.2, theta2=+0.2 (BE limits 0.80 - 1.20), exact
Note

Scripts for creation of these data.frame’s can be found in the \test sub-directory of the package. Comparing the results of that scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST

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**ct9.6.2+ct9.6.6**  
*Sample size tables for the 2x2x3 replicate crossover*

---

**Description**

These data.frames give sample size tables calculated with `samplenNtostHI` for the 2x2x3 replicate crossover design (2-treatment-2-sequence-3-period design).

**Details**

The data.frame’s can be accessed by their names or by `data("name")`.

- **ct9.6.2** is Table 9.6.2 from Chow S.C., Liu J.P.  
  "Design and Analysis of Bioavailability and Bioequivalence Studies",  
  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** is Table 9.6.6 from the same reference.  
  Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1), power via shifted non-central t-distribution.  
  Attention! Chow and Liu’s CV is se (standard error) of residuals.

Note

Scripts for creation of these data.frame’s can be found in the \test sub-directory of the package. Comparing the results of that scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST
Sample size tables for the 2x4x4 replicate crossover

**Description**

These data.frames give sample size tables calculated with `sampleN.TOST()` for the 2x4x4 replicate crossover design (2-treatment-4-sequence-4-period design).

**Details**

The data.frame’s can be accessed by their names or by `data("name")`.

Additive model, theta1=-0.2, theta2=+0.2 (BE limits 0.80 - 1.20), approximate power via shifted non-central t-distribution.

c9.6.8 is Table 9.6.8 from the same reference.
Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1), power via shifted non-central t-distribution.
Attention! Chow and Liu’s CV in case of multiplicative model is se (standard error) of residuals.

**Note**

Scripts for creation of these data.frame’s can be found in the \test sub-directory of the package.
Comparing the results of that scripts to the corresponding data.frames can be used for validation purposes.

**Author(s)**

PowerTOST

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.frame's can be accessed by their names or by `data("name")`.

`ctSJ.VIII.10` is Table VIII, column 'level of bioequivalence 10%' from S.A.Julious
"Tutorial in Biostatistics
Multiplicative model, theta1=0.9, theta2=1.1111 (1/theta1), target power=90%,
power approximate via non-central t-distribution.
Attention! Julious gives sample size per group.
`ctSJ.VIII.20` is Table VIII from the same source
column 'level of bioequivalence 20%'
Multiplicative model, theta1=0.8, theta2=1.25 (1/theta1), target power=90%,
power approximate via non-central t.

`ctCW.III` is Table III from Chow and Wang
"On Sample Size Calculation in Bioequivalence Trials"
Additive model, theta1=-0.2, theta2=+0.2 (BE limits 0.80 - 1.20), exact.

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

Note

Scripts for creation of these data.frame’s can be found in the `test` sub-directory of the package.
Comparing the results of that scripts to the corresponding data.frames can be used for validation purposes.

Author(s)

PowerTOST

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**Helper functions**

**Description**

Calculates the standard error or the mean squared error from a given CV and vice versa for log-normal data.
Usage

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

Arguments

CV            coefficient of variation
se            standard error
mse           mean squared error

Value

Returns se = sqrt(log(CV^2+1))
or CV = sqrt(exp(se*se)-1)
or mse = log(CV^2+1)
or 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*se)-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 chi-squared
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
- **df**: degrees of freedom of the CV (error variance)
- **side**: Side(s) to calculate the confidence limits for
- **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

```r
# upper one-sided 95% CL of a CV=0.3
# from a study with df=22 (f.i. a 2x2 crossover with n=24)
# side="upper" is standard if 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(point, lower, upper, n, design = "2x2", alpha = 0.05, robust=FALSE)`

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

point
Point estimator of the BE ratio.
The point estimator can 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.desig(n) for designs covered in this package.

alpha
Error probability. Set it to (1-confidence)/2.
Is 0.05 for the usual 90% confidence intervals.

robust
With robust=FALSE the 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.desig(n)) will be used. This may be helpful if the CI was evalu-
ated via mixed model or via intra-subject contrasts (aka Senn’s basic estimator).

Details

See Helmut Schuetz lectures at www.bebac.at/lectures.htm for a description of the algebra un-
derlying 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. greater than actually observed) in case of greater unbal-
ancedness.

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

Author(s)

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

# Given a 90% confidence interval (without point estimator)
# from a classical 2x2 crossover with 22 subjects
CV_from_CI(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/R.

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
**CVpooled**

**Examples**

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

**Description**

This function calculates a pooled CV from CV’s from several studies.

**Usage**

```r
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 2x2 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. Schuetz lectures [http://bebac.at/lectures/MU2010-CD2.pdf](http://bebac.at/lectures/MU2010-CD2.pdf)

- `logscale` Defaults to TRUE. Should the calculations be done for log-transformed data?

- `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’s are calculated as n-seq. They are also often more appropriate if the CV comes from a 'true' mixed 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 digits for CV.

- `verbose` Defaults to FALSE. Prints only the pooled CV and the 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 CV’s of the single studies, weights are the df (degrees of freedom).
If only \( n \) is given in the input \( CVdata \), the df’s 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 CV’s from parallel-group and cross-over 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 parallel group study, respectively.

Author(s)

D. Labes

References

H. Schuetz lectures about sample size challenges at http://bebac.at/lectures.htm.

Patterson, Jones
"Bioequivalence and Statistics in Clinical Pharmacology"
Chapter 5.7 "Determining Trial Size"
Chapman & Hall/CRC, Boca Raton 2006

See Also

\( known.designs, CVfromCI \)
Examples

# some data:
# the values for AUC, study 1 and study 2 are Example 3 of H. Schuetz lecture
CVs <- c("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 (replicate)"
)
txtcon <- textConnection(CVs)
CVdata <- read.table(txtcon, header=TRUE, sep="|", strip.white=TRUE, as.is=TRUE)
close(txtcon)

# evaluation of the AUC CV's
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 df's)
# Upper 80% confidence limit of CV = 0.266

---

exppower.noninf 'Expected' power of non-inferiority test

Description

Calculates the 'expected' power according to Julious for a variety of study designs used in bioequivalence studies.

Usage

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

Arguments

alpha Type I error probability, significance level. Defaults here to 0.025.

logscale Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.

theta0 'True' or assumed bioequivalence ratio or difference. Typically set to 0.95 (default if missing) if logscale=TRUE. Defaults to -0.05 if logscale=FALSE.
margin
Non-inferiority margin.
In case of logscale=TRUE it must be given as ratio, otherwise as diff.
Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.

CV
Coefficient of variation as ratio.

dfCV
Degrees of freedom for the CV (error/residual degree of freedom).

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.
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.

Details
This function calculates the so-called 'expected' power based on formulas according to S.A. Julious. These take into account that usually the CV is not known but estimated from a previous study / studies with an uncertainty. See references.

Value
Value of expected power according to the input.

Author(s)
D. Labes

References
S.A. Julious
"Sample sizes for Clinical Trials"
CRC Press, Chapman & Hall 2010

See Also
expsampleN.noninf, power.noninf, power.TOST

Examples
# expected power for non-inferiority test of a 2x2 crossover
# CV 30% known from a pilot study with 12 subjects (-> dfCV=10)
# using all the defaults for other parameters
# should give: [1] 0.6751358
exppower.noninf(CV=0.3, dfCV=10, n=40)

# Compare this to the usual power (CV known, "carved in stone")
# should give: [1] 0.7228685
gpower.noninf(CV=0.3, n=40)

exppower.TOST  'Expected' power of TOST procedure

Description

Calculates the so-called 'expected' power according to Julious for a variety of study designs used in bioequivalence studies.

Usage

exppower.TOST(alpha = 0.05, logscale=TRUE, theta0, theta1, theta2,
CV, dfCV, n, design = "2x2", robust=FALSE)

Arguments

alpha Level of significance. Commonly set to 0.05.

logscale Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.

theta0 'True' or assumed bioequivalence ratio or difference. Typically set to 0.95 (default if missing) if logscale=TRUE. Defaults to 0.05 if logscale=FALSE.

theta1 Lower bioequivalence limit as ratio if logscale=TRUE or as difference. Can be missing. Defaults then to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.

theta2 Upper bioequivalence limit as ratio if logscale=TRUE or as difference. If not given theta2 will be calculated as 1/theta1 if logscale=TRUE, else as -theta1.

CV Coefficient of variation as ratio.

dfCV Degrees of freedom for the CV (error/residual degree of freedom).

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. 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.
Details

This function calculates the so-called 'expected' power based on S.A. Julious taking into account that usually the CV is not known but estimated from a previous study / studies with an uncertainty. See references.

Value

Value of expected power according to the input.

Author(s)

D. Labes

References

S.A. Julious, R.J. Owen
"Sample size calculations for clinical studies allowing for uncertainty in variance"
Pharmaceutical Statistics (2006), 5, 29-37

S.A. Julious
"Sample sizes for Clinical Trials"
CRC Press, Chapman & Hall 2010

See Also

expsampleN.TOST, power.TOST

Examples

# expected power for a 2x2 crossover
# CV 30% known from a pilot study with 12 subjects (-> dfCV=10)
# using all the defaults for other parameters
# should give: [1] 0.7359771
exppower.TOST(CV=0.3, dfCV=10, n=40)

# Compare this to the usual power (CV known, "carved in stone")
# gives: [1] 0.8158453
power.TOST(CV=0.3, n=40)

Description

Calculates the sample size based on Julious 'expected' power for a variety of study designs used in bioequivalence studies. See known.designs() for the study designs covered.
Usage

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

Arguments

- **alpha**: Error probability. Typically set to 0.025 for one-sided test.
- **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**: 'True' or assumed bioequivalence ratio or difference. Maybe missing. Defaults then to 0.95 if \( \logscale=\text{TRUE} \) or to -0.05 if \( \logscale=\text{FALSE} \).
- **margin**: Non-inferiority margin. In case of \( \logscale=\text{TRUE} \) it must be given as ratio, otherwise as diff. Defaults to 0.8 if \( \logscale=\text{TRUE} \) or to -0.2 if \( \logscale=\text{FALSE} \).
- **CV**: Coefficient of variation as ratio. May be given as vector. Then the CV's were pooled as weighted mean (of s2) with their df (degrees of freedom) as weights.
- **dfCV**: Degrees of freedom for the CV's. Must be a vector of same length as CV.
- **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 \( n\text{-seq} \). See `known.designs()`$df2 for designs covered in this package.
- **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. Defaults to FALSE.
- **imax**: Maximum number of steps in sample size search. Defaults to 100. Adaption only in very rare cases needed. Never seen a need for adaption up to now.

Details

The sample size is calculated based on iterative evaluation of 'expected' power via Julious formulas based on non-central t-distribution. The start value of the sample size search is taken from a large sample approximation. The sample size is bound to 4 as minimum.

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 design implemented.
Author(s)
D. Labes

References
S.A. Julious
"Sample sizes for Clinical Trials"
CRC Press, Chapman & Hall, Boca Raton 2010

See Also
exppower.noninf, expsampleN.TOST

Examples

# Classical 2x2 cross-over, target power = 80%, alpha=0.025
# logscale=TRUE, 'non-superiority' margin 125%, assumed true BE ratio = 105%,
# intra-subject CV=30% estimated with 10 df
# using all the defaults
expsampleN.noninf(theta0=1.05, margin=1.25, CV=0.3, dfCV=10)
# -> gives n=56 with achieved expected power 0.807719
# Compare this to the usual sample size with CV known as 'carved in stone'
sampelen.ninf(theta0=1.05, margin=1.25, CV=0.3)

# More then one CV with corresponding degrees of freedom
# other parameters as above
CVs <- c(0.25, 0.3)
dfs <- c(22, 10)
expsampleN.noninf(theta0=1.05, margin=1.25, CV=CVs, dfCV=dfs)
# -> gives a pooled CV=0.2664927 with df=32
# and a sample size n=40 with achieved expected power 0.808157

Description
Calculates the sample size based on Julious 'expected' power for a variety of study designs used in bioequivalence studies. See known.designs() for the study designs covered.

Usage

expsampleN.TOST(alpha = 0.05, targetpower = 0.8, logscale=TRUE,
theta0, theta1, theta2, CV, dfCV, design = "2x2",
robust=FALSE, print = TRUE, details = FALSE, imax=100)
Arguments

alpha  Error probability. Typically set to 0.05.
targetpower  Power to achieve at least. Must be >0 and <1. Typical values are 0.8 or 0.9.
logs 
logscale  Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.
theta0  'True' or assumed bioequivalence ratio or difference.
Maybe missing. Defaults the to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE.
theta1  Lower bioequivalence limit as ratio if logscale=TRUE or as difference.
Can be missing. Defaults then to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
theta2  Upper bioequivalence limit as ratio if logscale=TRUE or as difference.
If not given theta2 will be calculated as 1/theta1 if logscale=TRUE, else as -theta1.
CV  Coefficient of variation as ratio.
May be given as vector. Then the CV’s were pooled as weighted mean with their df=degrees of freedom as weights.
dfCV  Degrees of freedom for the CV’s. Must be a vector of same length as CV.
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-2q.
See known.designs()$df2 for designs covered in this package.
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.
Defaults to FALSE.
imax  Maximum number of steps in sample size search.
Defaults to 100. Adaption only in very rare cases needed.
Never seen a need for adaption up to now.

Details

The sample size is calculated based on iterative evaluation of 'expected' power via Julious formulas based on non-central t-distribution.
The start value of the sample size search is taken from a large sample approximation.

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 design implemented.

Author(s)

D. Labes
known.designs

References

S.A. Julious, R.J. Owen
"Sample size calculations for clinical studies allowing for uncertainty in variance"
Pharmaceutical Statistics (2006), 5, 29-37

S.A. Julious
"Sample sizes for Clinical Trials"
CRC Press, Chapman & Hall, Boca Raton 2010

S. Senn
"Cross-over Trials in Clinical Research" Second edition
Wiley, Chichester 2002

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 with 10 df
# using all the defaults
expsampleN.TOST(CV=0.3, dfCV=10)
# -> gives n=48 with achieved expected power 0.805082
# Compare this to the usual sample size with CV known as 'carved in stone'
sampleN.TOST(CV=0.3)

# More then one CV with corresponding degrees of freedom
# other parameters as above
CVs <- c(0.25, 0.3)
dfs <- c(22, 10)
expsampleN.TOST(CV=CVs, dfCV=dfs)
# -> gives a pooled CV=0.2664927 with df=32
# and a sample size n=34 with achieved expected power 0.815019

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 will be used internal 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, Chow and Liu 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, Chow and Liu 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 (FDA model for replicate designs).

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

Author(s)

D. Labes
References

K.-W. Chen, S.-C. Chow and G. Liu
"A Note on Sample Size Determination for Bioequivalence Studies with Higher-order Crossover Designs"
J. Pharmacokinetics and Biopharmaceutics, Vol. 25, No. 6, p753-765 (1997)

S. Senn
"Cross-over Trials in Clinical Research"

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

Liu J-P
"Use of the Repeated Crossover design in Assessing Bioequivalence"

Examples

known.designs()

<table>
<thead>
<tr>
<th>OwensQ</th>
<th>Owen’s Q-function</th>
</tr>
</thead>
</table>

Description

Calculates Owen’s Q function.

Usage

OwensQ(nu, t, delta, a, b)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>nu</td>
<td>degree of Owen’s Q</td>
</tr>
<tr>
<td>t</td>
<td>parameter t</td>
</tr>
<tr>
<td>delta</td>
<td>parameter delta</td>
</tr>
<tr>
<td>a</td>
<td>lower integration limit</td>
</tr>
<tr>
<td>b</td>
<td>upper integration limit</td>
</tr>
</tbody>
</table>
Details
Uses `integrate()` from package stats to perform the numerical evaluation of the definite integral in Owen’s Q function.

See ./doc/BE_power_sample_size_excerpt.pdf in the package sub-directory/doc for the definition of Owen’s Q and implementation details.

In case of high delta and/or high upper integration limit b where the implementation via R’s function `integrate()` may fail the function `OwensQOwen()` is used.

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

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

Warning
Since for really large values of nu and the upper integration limit b the integrand is a function which is zero over nearly all its range, the `integrate()` function may fail (see `?integrate`) and `OwensQ()` then returns erroneously 0.

The function now tries to return a value via non-central t-approximation in such cases. This approximation is up to 6 decimals correct as far as tested.

`OwensQ()` issues a warning if the nct-approximation is used.

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

Author(s)
D. Labes

References
Owen, D. B. (1965)
"A Special Case of a Bivariate Non-central t-Distribution"
Biometrika, 52, 437-446.

See Also

OwensQOwen

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 in Owen’s original paper (Biometrika 1965) 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.
It is used in OwensQ() in case of high nu and/or high upper integration limit where the implementation via R’s function integrate() may fail. The implementation needs OwensT() function.

Author(s)
D. Labes

References
Owen, D.B. (1965)
"A Special Case of a Bivariate Non-central t-Distribution"
Biometrika Vol. 52, p437-446.
**OwensT**

**See Also**

OwensQ, OwensT

**Examples**

```r
# 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)
```

---

**Description**

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

**Usage**

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

**Arguments**

- `h` parameter h
- `a` upper limit of integration

**Details**

The function is simply implemented via stats function `integrate()`.

**Value**

Numeric value of the definite integral.

**Note**

This function is only needed in OwensQOwen(). But may be useful for others.

**Author(s)**

D. Labes

**See Also**

OwensQOwen, OwensQ
Examples

Owens(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, GMR, 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

```r
pa.ABE(CV, theta0 = 0.95, targetpower = 0.8, minpower = 0.7, design = "2x2", ...)
```

---

```r
## S3 method for class 'pwrA'
print(x, digits=4, plotit=TRUE, ...)
## S3 method for class 'pwrA'
plot(x, pct=TRUE, cols=c("blue", "red"), ...)
```

### Arguments

- **CV**
  - Coefficient of variation 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.

- **theta0**
  - 'True' or assumed bioequivalence 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 many sense.
  - If package run under R version < 3.1.0 targetpower has to be > 0.5.

- **minpower**
  - Minimum acceptable power to have if deviating from assumptions for sample size plan.
  - Has to be < as targetpower. Defaults to 0.7.
  - minpower or targetpower < 0.5 doesn't make many sense.
  - If package run under R version < 3.1.0 minpower has to be >= 0.5.

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

---

More arguments to pass to `power.TOST()`. For instance, `alpha`, `theta1`, `theta2` or `robust` if other values than 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:
Object of class 'pwrA'.

Digits for rounding power in printing. The '...' argument is currently ignored in print().

If set to TRUE, the default, the print method calls print(x) if R is running interactively.

If set to TRUE (the default) scales CV and power in percent in print(). Else they will be given as ratios, the usual standard in PowerTOST.

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, 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 demanded 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's upto you to decide on reasonable combinations and analyze the power of them.

Value

Returns a list with class "pwrA" with the components

A data.frame with the result of the sample size estimation. See output of sampleN.TOST().

A data.frame with value pairs CV, pwr for impact of deviations from CV.

A data.frame with value pairs theta0, pwr for impact of deviations from theta0 (GMR).

A data.frame with value pairs N, pwr for impact of deviations from planned N (drop-outs).

Method of BE decision. Here fix = "ABE".

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 drop of power than more extreme drop-out patterns.

Author(s)

Idea and original code by Helmut Schuetz
with modifications by D. Labes to use PowerTOST infrastructure.
References


See Also

power.TOST, known.designs, pa.scABE

Examples

# using the defaults
# design="2x2", targetpower=0.8, minpower=0.7, theta0/GMR=0.95
# BE acceptance range from defaults of sampleN.TOST() 0.8 ... 1.25
# print & plot implicit
pa.ABE(CV=0.2)
# print & plot
## Not run:
res <- pa.ABE(CV=0.2)
print(res, plotit=FALSE) # print only
plot(res)
## End(Not run)

pa.NTIDFDA

Power analysis for scaled ABE for NTID according to FDA

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 (NTID) 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 Warfarin guidance.

Usage

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

Arguments

CV

Coefficient of variation of the intra-subject viabilities of Test and Reference as ratio.
Here only the case CVwT=CVwR is implemented, i.e. CV has to be a scalar.

theta0

'True' or assumed bioequivalence 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 many 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 many sense.

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

Details

Power calculations are done via power.NTIDFDA() and calculations of CV and theta0 which result in minpower are derived via 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 into account as demanded in most BE guidances.

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’s upto you to decide on reasonable combinations and analyze the power of them.

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.NTIDFDA()

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 (drop-outs).

method Method of BE decision. Here fix = "NTID FDA".

regulator Here fix = "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 extremly 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 drop of power than more extreme drop-out patterns.

Author(s)

D. Labes
according to code by Helmut Schuetz for pa.ABE() and pa.scABE()

References

FDA "Draft Guidance on Warfarin Sodium"
Recommended Dec 2012

See Also

power.NTIDFDA, pa.ABE, pa.scABE print.pwrA, plot.pwrA

Examples

# using the defaults:
# targetpower=0.8, minpower=0.7, theta0/GMR=0.975
# BE acceptance range from defaults of sampleN.NTIDFDA() 0.8 ... 1.25
# 1E5 sims in power.NTIDFDA()
# not run due to timing policy of CRAN for examples
# may run some ten seconds or more
## Not run:
plot(pa.NTIDFDA(CV=0.1))
## End(Not run)

---

**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

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

CV
Coefficient of variation of the intra-subject variability as ratio.
Here only the case CVwT=CVwR is implemented, i.e. CV has to be a scalar.

theta0
'True' or assumed bioequivalence ratio. Often named GMR.
Must be given as ratio. Defaults to 0.9 here since HVD have a greater scatter in point estimator 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.
targetpower < 0.5 doesn’t make many sense.
If package run under R version < 3.1.0 targetpower has to be >= 0.5.

minpower
Minimum acceptable power to have if deviating from assumptions for sample size plan.
Has to be < as targetpower. Defaults to 0.7.
minpower or targetpower <0.5 does`nt make many sense.
If package run under R version < 3.1.0 minpower has to be >= 0.5.

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, ANVISA or FDA.
Defaults to EMA, method of scaled (widened) bioequivalence limits.

... More arguments to pass to power.scABEL() or power.RSABE().
F.i. alpha, theta1, theta2 or nsims if other values then 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 are derived via 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 demanded 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’s upto you to decide on reasonable combinations and analyze the power of them.

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 (drop-outs).

method  Method of BE decision. Here fix = "scABE".

regulator  "EMA" 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 drop of power than more extreme drop-out patterns.

Author(s)

Idea and original code by Helmut Schuetz with modifications by D. Labes to use PowerTOST infrastructure.

References


See Also

power.scABEL, power.RSABEL, print.pwrA, plot.pwrA, pa.ABE

Examples

# using the defaults:
# design="2x3x3", targetpower=0.8, minpower=0.7, theta0/GMR=0.90
# BE acceptance range from defaults of sampleN.scABEL() 0.8 ... 1.25
# 1E5 sims in power.scABEL()
# not run due to timing policy of CRAN, may run some ten seconds
## Not run:
# implicit print & plot
pa.scABEL(CV=0.4)
## End(Not run)
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, theta1, theta2, theta0, CV, n, rho, design = "2x2", robust = FALSE, setseed = TRUE)

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 or on original scale? TRUE or FALSE. Defaults to TRUE.

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 parameters under consideration. This is defined as correlation between the estimator of the treatment difference of parameter one and the estimator of the treatment difference of parameter two.

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.desigs()$df2 for designs covered in this package. Has only effect for higher-order crossover designs.

setseed Calculation depends on pmvt() which is based on randomized quasi Monte Carlo methods. If setseed=TRUE a seed value is set, the default.

Details

The exact calculations of the power are performed via integration of the 4-dimensional non-central t-distribution via function pmvt() of package mvtnorm. An absolute error tolerance of 1e-04 is set within pmvt().

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)

Benjamin Lang

References

Hua S. Y., Xu S., and D’Agostino Sr. R. B.
"Multiplicity adjustments in testing for bioequivalence"
"Letter to the Editor 'Comments on Multiplicity adjustments in testing for bioequivalence'".
Statistics in Medicine.

"Power for Testing Multiple Instances of the Two One-Sided Tests Procedure"
The International Journal of Biostatistics: Vol. 5: Iss. 1, Article 15.

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: [1] 0.3981441

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

Description
Power of dose-proportionality studies evaluated via Power model

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. Usually taken as 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 values. At least 2 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 (Rdmm). Transforms into slope acceptance range as described under item beta0.
theta2  Upper acceptance limit for the ratio of dose normalized means (Rdmm).
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 bibNclHI.
cvb     Coefficient of variation of the between-subject variability. Only necessary if design="IBD". Will be set to 2*CV if missing. 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 alternative 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="crossover" 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"
Chapman & Hall/CRC, Boca Raton, 2006, page 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"
Hummel J, McKendrick S, Brindley C, and R French
"Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion"

See Also
sampleN.dp, bib.CL

Examples

# using all the defaults, i.e. latin square crossover design, alpha=0.05,
# beta=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 NTID's

Description

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

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. 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 bioequivalence ratio. Defaults to 0.95 if not given explicitly.
CV Coefficient(s) of variation as ratio. If length(CV) = 1 the same CV is assumed for Test and Reference. If length(CV) = 2 the CV for Test must be given in CV[1] and for Reference in 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 n’s 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. 2x2x3 is the 3-period 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-ratio) 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-ratio) is the power of the criterion 'ratio of sWT/sWR is <= 2.5' alone.
Note
The FDA guidances recommend only the full replicate design 2x2x4. The results for the design
"2x2x3" are to be considered as experimental since at present not thoroughly tested.

Author(s)
D. Labes

References
FDA "Draft Guidance on Dabigatran Etexilate Mesylate"
Recommended Jun 2012; Revised Sept 2015
FDA "Draft Guidance on Rivaroxaban"
Recommended Sept 2015

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

Examples
```r
# using the defaults:
# GMR=0.95, theta1=0.8, theta2=1.25, full replicate design 2x2x4, 100 000 sims
# 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**
```r
power.noninf(alpha = 0.025, logscale = TRUE, margin, theta0, CV, n,
             design = "2x2", robust = FALSE)
```
Arguments

alpha  Type I error probability, significance level. Defaults here to 0.025.

logscale  Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.

margin  Non-inferiority margin.
In case of logscale=TRUE it must be given as ratio, otherwise as diff. to 1.
Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.

theta0  'True' or assumed bioequivalence ratio or difference.
In case of logscale=TRUE it must be given as ratio,
otherwise as difference to 1. See examples.
Defaults to 0.95 if logscale=TRUE or to -0.05 if logscale=FALSE.

CV  Coefficient of variation 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 df are calculated as nMseq.
See known.designs$df2 for designs covered in this package.
Has only effect for higher-order crossover designs.

Details

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

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'.
Author(s)
D. Labes

References
S.A. Julious
"TUTORIAL IN BIOSTATISTICS
Sample sizes for clinical trials with Normal data"

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.NTIDFDA  (Empirical) Power for BE decision via FDA method for NTID's

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

Usage
power.NTIDFDA(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 bioequivalence ratio. Attention! Defaults here to 0.975 if not given explicitly. The value was chosen nearer to 1 because the potency (contents) settings for NTID's are tightened by the FDA.
CV
Coefficient(s) of variation as ratio.
If length(CV) = 1 the same CV is assumed for Test and Reference.
If length(CV) = 2 the CV for Test must be given in CV[1] and for Reference in 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 n’s 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.
2x2x3 is the 3-period 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-sABEc) is the probability that the 95% CI of the ABE criterion is <0.
p(BE-sratio) is the probability that 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
The linearized scaled ABE criterion is calculated according to the SAS code given in the FDA Warfarin guidance. For deciding BE the study must pass that criterion, the conventional ABE test 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 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.
p(BE) is the 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 ‘ratio of sWT/sWR is <= 2.5’ alone.

**Note**

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 thoroughly tested.

**Author(s)**

D. Labes

**References**

FDA "Draft Guidance on Warfarin Sodium"
Recommended Dec 2012

LX Yu et al.
"Novel bioequivalence approach for narrow therapeutic index drugs"
Article first published online: 15 DEC 2014

W Jiang et al.
"A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion"
The AAPS Journal, July 2015, Volume 17, Issue 4, pp 891-901
First online: 04 April 2015

Laszlo Endrenyi and Laszlo Tothfalusi
"Determination of Bioequivalence for Drugs with Narrow Therapeutic Index: Reduction of the Regulatory Burden"

**See Also**

`sampleN.NTIDFDA`
and `power.HVNTID, sampleN.HVNTID` for NTIDs with high variability

**Examples**

```r
# using the all defaults:
# GMR=0.975, theta1=0.8, theta2=1.25, 100000 sims
# and a CV of 0.1 (= 10%) with 12 subjects, balanced
power.NTIDFDA(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 (again a TOST procedure).

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 (‘null’) assumed bioequivalence 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() from 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. In such studies the 95% confidence intervals are usually used for equivalence testing. Therefore alpha defaults here to 0.025. See CPMP/EWP/482/99 "Points to consider on switching between superiority and non-inferiority" EMEA, London (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 2x2 crossover design.

Author(s)

D. Labes

References


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
Description

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

Usage

```r
power.RSABE(alpha = 0.05, theta1, theta2, theta0, CV, n,
             design = c("2x3x3", "2x2x4", "2x2x3"), regulator = c("FDA", "EMA"),
             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 estimator 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 estimator constraint. Defaults to 1.25 if not given explicitly.
- `theta0`: 'True' or assumed bioequivalence ratio. Defaults to 0.95 if not given explicitly.
- `CV`: Coefficient(s) of variation as ratio.
  - If `length(CV) = 1` the same CV is assumed for Test and Reference.
  - If `length(CV) = 2` the CV for Test must be given in CV[1] and for Reference in 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 (TRTR|RTR) design the order of n’s 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".
**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 criterion.
Details can be found in a document "Implementation_scaledABE_simsVx.yy.pdf" 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-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.

**Warning**

In case of the design 2x2x3 heteroscedasticity (CVwT not equal to CVwR) may lead to poor agreement of the power values compared to those calculated via the 'classical' way of subject data sims if the design is unbalanced in respect to the number of subjects in the sequence groups. The function therefore issues a warning for that cases.

**Author(s)**

D. Labes
References

FDA "Draft Guidance on Progesterone"
Recommended Apr 2010; Revised Feb 2011

Laszlo Tothfalusi and Laszlo Endrenyi
"Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs"

Tothfalusi L., Endrenyi L. and A. Garcia Arieta
"Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence"

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 =0.95, 1E+5 simulations
power.RSABE(CV=0.4, n=24)
# should give
# [1] 0.80864
#
# to explore the simulation error due to the state of the
# random number generator
power.RSABE(CV=0.4, n=24, setseed=FALSE)
# will give something like
# [1] 0.8081

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

Description

This 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 = c("EMA", "ANVISA", "FDA"),
       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 estimator 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 estimator constraint.
Defaults to 1.25 if not given explicitly.

**theta0**
'True' or assumed bioequivalence ratio.
Defaults to 0.95 if not given explicitly.

**CV**
Coefficient(s) of variation as ratio.
If length(CV) = 1 the same CV is assumed for Test and Reference.
If length(CV) = 2 the CV for Test must be given in CV[1] and for Reference in 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 n’s 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".

**regulator**
Regulatory body settings for the widening of the BE acceptance limits.
Defaults to regulator="EMA".
This argument may be given also in lower case.

**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.
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

\[ \text{LBEL,UBEL} = \exp(-r_{\text{const}} s_{WR}) \]

with \( r_{\text{const}} \) the regulatory constant and \( s_{WR} \) the standard deviation of the within subjects variability of the Reference. \( r_{\text{const}}=0.76 \) is used in case of \( \text{regulator} = \text{EMA} \) and in case of \( \text{regulator} = \text{FDA} \) \( r_{\text{const}}=0.89257...=\log(1.25)/0.25 \). If the CV\( wR \) of the Reference is < CV\( \text{switch}=0.3 \) the conventional ABE limits apply (mixed procedure). In case of \( \text{regulator} = \text{EMA} \) a cap is placed on the widened limits if CV\( wR > 0.5 \), i.e. the widened limits are held at value calculated for CV\( wR=0.5 \). In case of \( \text{regulator} = \text{ANVISA} \) the EMA settings are used but CV\( \text{switch}=0.3 \) is used. See http://forum.bebac.at/mix_entry.php?id=14877

The simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on widened ABEL.

For more details see a document "Implementation_scaledABE_simsVx.yy.pdf" in the /doc subdirectory of the package.

Value

Returns the value of the (empirical) power if argument \texttt{details=FALSE}.

Returns a named vector if argument \texttt{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.

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.

The function therefore gives a warning if calculations with different CV\( wT, CVwR \) are requested for the 2x3x3 partial replicate design.

For more details see the above mentioned document "Implementation_scaledABE_simsVy.xx.pdf"

Note

In case of \( \text{regulator} = \text{FDA} \) the (empirical) power is only approximate since the BE decision method is not exactly what is expected by the FDA. But the two Laszlos 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 \( \text{powerNrsabeHI} \).

Author(s)

D. Labes
power.TOST

References

Laszlo Tothfalusi and Laszlo Endrenyi
"Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs"

See Also

sampleN.scABEL, power.RSABE

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 =0.95, 1e+6 simulations
power.scABEL(CV=0.4, n=29)
# should give:
# Unbalanced design. n(i)=10/10/9 assumed.
# [1] 0.82854
# with details=TRUE to view the computational time
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

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 Type I error probability, significance level. By convention mostly set to 0.05.
logscale Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.
theta1 Lower bioequivalence limit.
In case of logscale=TRUE it is given as ratio, otherwise as diff. to 1. Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
theta2
Upper bioequivalence limit.
If not given theta2 will be calculated as 1/theta1 if logscale=TRUE or as -theta1 if logscale=FALSE.

theta0
'True' or assumed bioequivalence ratio.
In case of logscale=TRUE it must be given as ratio, otherwise as difference to 1. See examples.
Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE.

CV
Coefficient of variation 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="pmvt". 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 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
The exact calculations of power are based on Owen's Q-function or via direct integration of the bivariate non-central t-distribution via function pmvt() of package mvtnorm.
The approximate power is implemented via non-central t-distribution or via 'shifted' central t-distribution.
The formulas cover now 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 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 mes-
sage 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.

Former function power2.*TOST()* design to handle unbalanced studies is now removed since power.*TOST()* handles balanced as well as unbalanced designs.

Author(s)

D. Labes
Direct integration of bivariate non-central t-distribution by Benjamin Lang.

References

"Power of the Two One-Sided Tests Procedure in Bioequivalence"
J. of Pharmacokinetics and Biopharmaceutics, 18, 137-144.
"Sample Size Determination for Bioequivalence Assessment by Means of Confidence Intervals"
Int. J. of Clinical Pharmacology, Therapy and Toxicology, 29, 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.TOST.sim

# 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 of the TOST procedure obtained via simulations

Description

Power is calculated by simulations of studies (PE via it’s normal distribution, MSE via it’s associated chi-squared distribution) and application of the two one-sided t-tests. Power is obtained via ratio of studies found BE to # of simulated studies.

Usage

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

Arguments

- **alpha**: Type I error probability, significance level. By convention mostly set to 0.05.
- **logscale**: Should the data used on log-transformed or on original scale? TRUE or FALSE. Defaults to TRUE.
- **theta1**: Lower bioequivalence limit.
  In case of logscale=TRUE it is given as ratio, otherwise as diff. to 1. Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
- **theta2**: Upper bioequivalence limit.
  If not given theta2 will be calculated as 1/theta1 if logscale=TRUE or as -theta1 if logscale=FALSE.
- **theta0**: ‘True’ or assumed bioequivalence ratio.
  In case of logscale=TRUE it must be given as ratio, otherwise as difference to 1. See examples.
  Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE
- **CV**: Coefficient of variation 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 df are calculated as n-seq. See known.desig{}ns()$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 set.seed=TRUE, the default. Set this argument to FALSE to view the variation in power between different runs.

nsims

Number of studies to simulate. Default to 1E5 = 100 000.

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

\textit{p-value(s) of the TOST procedure}

\textbf{Description}

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

\textbf{Usage}

\begin{verbatim}
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)
\end{verbatim}

\textbf{Arguments}

- \textit{pe}  
  Observed point estimator of the ratio Test vs. Reference (if \texttt{logscale=TRUE}) or of the difference (if \texttt{logscale=FALSE}).

- \textit{CV}  
  Observed coefficient of variation as ratio or error standard deviation.

- \textit{n}  
  Total number of subjects if given as scalar. Number of subjects in (sequence) groups if given as vector.

- \textit{logscale}  
  Should the data used after log-transformation or on original scale? \texttt{TRUE} or \texttt{FALSE}. Defaults to \texttt{TRUE}. \texttt{logscale=FALSE} is useful if you have the data of analysis after log-transformation only.

- \textit{theta1}  
  Lower bioequivalence limit. In case of \texttt{logscale=TRUE} it has to be given as ratio, otherwise as value < 0. Defaults to 0.8 if \texttt{logscale=TRUE} or to \texttt{log(0.8)=-0.2231} if \texttt{logscale=FALSE}.

- \textit{theta2}  
  Upper bioequivalence limit. If not given \textit{theta2} will be calculated as \texttt{1/theta1} if \texttt{logscale=TRUE} or as \texttt{-theta1} if \texttt{logscale=FALSE}.

- \textit{design}  
  Character string describing the study design. See \texttt{known.designs()} for designs covered in this package.

- \textit{robust}  
  If set to \texttt{TRUE} triggers the use of degrees of freedom according to the ‘robust’ evaluation (aka Senn’s basic estimator). These \textit{df} are calculated as \texttt{n-seq}. See \texttt{known.designs()}$df2.Has only effect for higher-order crossover designs. Defaults to \texttt{FALSE}. With that value the usual degrees of freedom will be used.

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

value.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 names the p-value of testing HA1: theta>=theta1, 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)
Benjamin 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"
Hauschke D, Steinijans V, Pigeot I
"Bioequivalence Studies in Drug Development"
John Wiley & Sons Ltd, Chichester 2007

See Also
CI.BE

Examples
# Defaults: 2x2 crossover, log-transformation
# BE acceptance limits 0.8 ... 1.25, usual df's
# 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
sampleN.2TOST

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=0.333, n=24)
# lower limit = 0.7766 outside 0.8 ... 1.25, i.e inequivalence can't be rejected

---

**Sample size based on power of 2 TOSTs**

**Description**

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

**Usage**

```r
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)
```

**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 or FALSE. Defaults to TRUE.
- `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.
- `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 parameters under consideration. This is defined as correlation between the estimator of the treatment difference of parameter one and the estimator of the treatment difference of parameter two.
**sampleN.2TOST**

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

- **setseed**
  Calculation depends on `pmvt()` which is based on randomized quasi Monte Carlo methods. If `setseed=TRUE` a seed value is set, the default.

- **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 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.

**Details**

The sample size is calculated via iterative evaluation of power of the 2 TOSTs. Start value for the sample size search is taken from a large sample approximation (1 TOST) according to Zhang, modified. The sample size is bound to 4 as minimum.

**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 CV’s f.i. use 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)**

Benjamin Lang
References

Hua S. Y., Xu S., and D’Agostino Sr. R. B.
"Multiplicity adjustments in testing for bioequivalence"

"Letter to the Editor 'Comments on Multiplicity adjustments in testing for bioequivalence’". Statistics in Medicine.

Zhang P.
"A Simple Formula for Sample Size Calculation in Equivalence Studies"

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=0.808840
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=0.801250
sampleN.2TOST(logscale=FALSE, theta0 = rep(-0.05, 2), CV = c(0.2, 0.2),
rho = 0.9, design = "parallel")

---

Sample size estimation of dose-proportionality studies evaluated via
Power model

Description

Performes a sample size estimation for dose-proportionality studies using the Power model for
crossover (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, CVD, print = TRUE, details = FALSE, imax = 100)
```
Arguments

alpha
Type 1 error. Usually taken as 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 2 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' slope of power model. If missing defaults to \(1+\log(0.95)/\log(rd)\)
where rd is the ratio is the ratio of highest to lowest dose.
Has to be within slope acceptance range according to \(1+\log(\theta_1)/\log(rd)\)
and \(1+\log(\theta_2)/\log(rd)\). 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).

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 IBD described in Chow, Liu’s book "Design and Analysis of Bioavailability and Bioequivalence Studies".

CVb
Coefficient of variation of the between-subject variability.
Only necessary if design="IBD". Will be set to 2*CV if missing.
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 calculated 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.

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

Patterson, Jones
"Bioequivalence and Statistics in Clinical Pharmacology"
Chapman & Hall/CRC, Boca Raton, 2006, page 239
(contains presumably a bug)

Hummel J, McKendrick S, Brindley C, and R French
"Exploratory assessment of dose proportionality: review of current approaches and proposal for a practical criterion"
Pharmaceut Statist 8(1), 38-49 (2009)

Sethuraman VS, Leonov S, Squassante L, Mitchell TR, Hale MD
"Sample size calculation for the Power Model for dose proportionality studies"

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

## Not run:
# incomplete block design mentioned in Sethuraman et al.
# with 5 doses, 20 sequences, 3 periods
# (I hope at least that the design is that they used)
library(crossdes)
# IBD based on mutually orthogonal Latin squares
ibd <- des.MOLS(trt=5, k=3)
CVb <- mse2CV(0.8) # Sethuraman et al. omega squared
sampleN.dp(CV=0.2, doses=c(5, 25, 50, 100, 200), beta0=1, design="IBD", dm=ibd, CVb=CVb)
# power of that design near 90% with n=30, sequence group unbalanced
power.dp(CV=0.2, doses=c(5, 25, 50, 100, 200), n=30, beta0=1, design="IBD", dm=ibd, CVb=CVb)
## End(Not run)
Sample size estimation for BE decision via FDA method for highly variable (HV) narrow therapeutic index drugs (NTID's)

Description

This function performs the Sample size estimation for the BE decision via FDA method for highly variable NTID's as described in the FDA Dabigatran / Rivaroxaban guidances based on simulations. The study designs may be the full replicate design 2x2x4 with 4 periods and the 3-period replicate design 2x2x3 with sequences RTR|TRT.

Usage

```r
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 bioequivalence 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**: Coefficient(s) of variation as ratio. If length(CV) = 1 the same CV is assumed for Test and Reference. If length(CV) = 2 the CV for Test must be given in CV[1] and for Reference in CV[2].
- **design**: Design of the study to be planned. 2x2x4 is the full replicate design with 2 sequences and 4 periods. 2x2x3 is the 3-period replicate design with sequences TRT|TRT. 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 \( \leq 2.5 \).

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 now 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 \( n=6 \), even if the power is higher than the intended targetpower.

Author(s)

D. Labes

References

FDA "Draft Guidance on Dabigatran Etexilate Mesylate"
Recommended Jun 2012; Revised Sept 2015
Sample size for the non-inferiority t-test

Description

Function for calculating 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

```r
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**: Type I error probability, significance level. 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.
- **margin**: Non-inferiority margin. In case of logscale=TRUE it must be given as ratio, otherwise as diff. to 1. Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.
theta0 'True' or assumed bioequivalence ratio or difference.
In case of logscale=TRUE it must be given as ratio,
otherwise as difference to 1. See examples.
Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE

CV Coefficient of variation 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.

Value
A data.frame with the input 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 CV's f.i. use for-loops or the apply-family.

Author(s)
D. Labes

References
S.A. Julious
"TUTORIAL IN BIOSTATISTICS
Sample sizes for clinical trials with Normal data"
sampleN.NTIDFDA

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

**Sample size estimation for BE decision via FDA method for narrow therapeutic index drugs (NTID's)**

**Description**

This function performs the Sample size estimation for the BE decision via FDA method for NTID’s based on simulations. The study design is the full replicate design 2x2x4 or the 3-period replicate design with sequences TRT|RTR.

**Usage**

```r
sampleN.NTIDFDA(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 bioequivalence ratio. Attention! Defaults here to 0.975 if not given explicitly. The value was chosen nearer to 1 because the potency (contents) settings for NTID’s 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
Coefficient(s) of variation as ratio.
If length(CV) = 1 the same CV is assumed for Test and Reference.
If length(CV) = 2 the CV for Test must be given in CV[1] and for Reference
in CV[2].

design
Design of the study to be planned.
2x2x4 is the full replicate design with 2 sequences and 4 periods.
2x2x3 is the 3-period 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.

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
The linearized scaled ABE criterion is calculated according to the SAS code given in the FDA War-
farine guidance. For deciding BE the study must pass that criterion, the conventional ABE test 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 these method.
Details can be found in a document "Implementation_scaledABE_sims" located in the doc subdi-
rectory of the package.

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 event-
ually also fail since the start values chosen may not really reasonable for them. This applies es-
pecially for theta0 values near to the implied scaled (tightened/widened) ABE limits according to
exp(+1.053605*swR).
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 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 results for the design "2x2x3" are to be considered as experimental since at present not thoroughly tested. The minimum sample size is n=6, even if the power is higher than the intended targetpower.

Author(s)

D. Labes

References

- FDA "Draft Guidance on Warfarin Sodium"
  Recommended Dec 2012
- LX Yu et al.
  "Novel bioequivalence approach for narrow therapeutic index drugs"
  First published online: 15 DEC 2014
- W Jiang et al.
  "A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion"
  The AAPS Journal, July 2015, Volume 17, Issue 4, pp 891-901
  First published online: 04 April 2015

See Also

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

Examples

```r
sampleN.NTIDFDA(CV=0.04,theta0=0.975)
# should give
# n=54 with an (empirical) power of 0.809590
#
# Test formulation with lower variability
sampleN.NTIDFDA(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.NTIDFDA(CV=0.04,theta0=0.975, design="2x2x3")
# should give
```

Description

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

Usage

```r
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 ('null') assumed bioequivalence 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 \texttt{pmvt()} from the package \texttt{mvtnorm}. Due to the calculation method used in package \texttt{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 $\frac{\text{MS(subject within sequence)}-\text{MS(error)}}{2}$.

Value

A data.frame with the input values and results will be returned. The sample size \( n \) returned is the \textbf{total} sample size for \textbf{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.


Author(s)

D. Labes

References


See Also

\texttt{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**

```r
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 bioequivalence ratio. Defaults to 0.90 according to the two Laszlo's 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 estimator 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 estimator constraint. Defaults to 1.25 if not given explicitly.
**CV**

Coefficient(s) of variation as ratio.  
If \( \text{length}(\text{CV}) = 1 \) the same CV is assumed for Test and Reference.  
If \( \text{length}(\text{CV}) = 2 \) the CV for Test must be given in CV[1] and for Reference in CV[2].

**design**

Design of the study to be planned.  
2x3x3 is the partial replicate design (TRRIRTRRRT).  
2x2x4 is the full replicate design with 2 sequences and 4 periods.  
2x2x3 is the 3-period design with sequences (TRTRTR).  
Defaults to `design"2x3x3"`.

**regulator**

Regulatory body settings for the scaled ABE criterion.  
Defaults to `regulator"FDA"`.  
Also the scaled ABE criterion is usually calculated with the FDA constant \( r_{\text{const}}=\log(1.25)/0.25 \) you can override this behavior to use the EMA setting \( r_{\text{const}}=0.76 \) to avoid the discontinuity at \( \text{CV}=30\% \) 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 seldom 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 progestosterone 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.

**Value**

Returns now 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.

**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 \( \text{CV} = 0.3 \) 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**

FDA "Draft Guidance on Progesterone"
Recommended Apr 2010; Revised Feb 2011

Lászlo Tóthfalusi and Lászlo Endrényi
"Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs"

Tóthfalusi L., Endrényi L. and A. Garcia Arieta
"Evaluation of Bioequivalence for Highly Variable Drugs with Scaled Average Bioequivalence"

**See Also**

`power.RSABE`, `power.scABEL`

**Examples**

```r
# 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 sims
sampleN.scABEL(CV=0.3)
# results in a sample size n=45, power=0.80344
```

---

**sampleN.scABEL**

*Sample size estimation for BE decision via scaled (widened) BE acceptance limits*

**Description**

This function performs the Sample size estimation for the BE decision via scaled (widened) 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 = c("EMA", "ANVISA", "FDA"),
    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 bioequivalence ratio. Defaults to 0.90 according to the two Laszlo's 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 estimator 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 estimator constraint. Defaults to 1.25 if not given explicitly.
- **CV**: Coefficient(s) of variation as ratio. If length(CV) = 1 the same CV is assumed for Test and Reference. If length(CV) = 2 the CV for Test must be given in CV[1] and for Reference in CV[2].
- **design**: Design of the study to be planned. 2x3x3 is the partial replicate design (TRRIRTRRRT). 2x2x3 is the 3-period replicate design (TRTIRTR). 2x2x4 is the full replicate design with 2 sequences and 4 periods. Defaults to design="2x3x3".
- **regulator**: Regulatory body settings for the widening of the BE acceptance limits. Defaults to regulator="EMA". This argument may be given also in lower case.
- **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 seldom needed.
- **imax**: Maximum number of steps in sample size search. Defaults to 100.
- **print**: If TRUE (default) the function prints its results.
- **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 simulations are done via the distributional properties of the statistical quantities necessary for deciding BE based on widened ABEL. For more details see a document in the doc subdirectory of the package.

Value

Returns now 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.

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. 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 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.

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 Laszlo's state that the scABEL method should be 'operational' equivalent to the FDA method. Thus the sample size should be comparable.
Consider in case of regulator="FDA" to use the function sampleN.RSABE().
The minimum sample size is n=6, even if the power is higher than the intended targetpower.

Author(s)

D. Labes

References

Lászlo Tóthfalusi and Lászlo Endrényi
"Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs"

See Also

data.scABEL, power.scABEL, sampleN.scABEL
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

```r
sampleN.scABEL(alpha = 0.05, targetpower = 0.8, theta0, theta1, theta2, CV = 0.3, design = c("2x3x3", "2x2x4", "2x2x3"), regulator = c("EMA", "ANVISA"), nstart = NA, nsims = 1e6, imax=100, print = TRUE, details = FALSE, alpha.pre = 0.05, setseed = TRUE)
```

Arguments

- **alpha**: Type I error (TIE) probability (nominal level of the test). Per convention commonly set to 0.05. A lower value might be specified (e.g., in order to adjust for multiplicity in dose proportionality studies).
- **targetpower**: Power to achieve at least. Must be `{=>0, <=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 bioavailability ratio. Defaults to 0.90 if not given explicitly.
theta1  Conventional lower ABE limit to be applied in the mixed procedure if \( CV_{WR} = CV_{SWITCH} \). 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 \( CV_{WR} = CV_{SWITCH} \). Also upper limit for the point estimate constraint.

Defaults to 1.25 if not given explicitly.

CV  Coefficient(s) of variation as ratio (not percent). Defaults to 0.30 (i.e., the location of maximum inflation of the TIE for the EMA’s ABE).

If \( \text{length}(CV) = 1 \) the same CV of Test and Reference is assumed (\( CV_{WT} = CV_{WR} \)).

If \( \text{length}(CV) = 2 \) the CV of Test must be given in \( CV[1] \) and the one of Reference in \( CV[2] \).

design  Design of the study to be planned.

"2x3x3" is the partial replicate design (RRT|RTR|TRR).

"2x2x3" is the 2-sequence 3-period full replicate design (RTR|TRT).

"2x2x4" is the 2-sequence 4-period full replicate design (RTRT|TRTR).

Defaults to design = "2x3x3".

regulator  Regulatory body settings for expanding the BE acceptance limits.

Defaults to regulator = "EMA".

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 \( \alpha_{N-pre} \), if given), \( \theta_0 \), and \( \text{targetpower} \).

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.

print  If TRUE (default), the function prints its results.

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. ABE 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. Not recommended for \( CV_{WR} >= 0.45 \) 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 a set.seed(123456) is issued if setseed=TRUE (default).

**Details**

The simulations are done via the distributional properties of the statistical quantities necessary for assessing BE based on ABE.
Simulations for the TIE are performed at the upper (expanded) limit $U$ of the acceptance range. Examples of $U$ at EMA’s CVswitch and CVcap:

```r
scABEL(CV=0.3, regulator="EMA")[["upper"]]
[1] 1.25
scABEL(CV=0.5, regulator="EMA")[["upper"]]
[1] 1.43191
```

Due to the symmetry around 1 results are valid for the lower (expanded) limit $L$ as well.

If a significant inflation of the TIE is expected (i.e., exceeding 0.05036 for one million simulations), alpha is iteratively adjusted until at least the target power is reached and the consumer risk is maintained (n.s. $>\alpha_0$).

The significance limit is based on the one sided binomial test, e.g.,

```r
binom.test(0.05*1e6, 1e6, alternative="less", conf.level=1-0.05)$conf.int[2]
```

**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 “adj. alpha” column and other results are identical to the ones obtained by `sampleN.scABEL`.

**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.

**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.

In case of regulator="ANVISA" no official guidance exists. There is a discontinuity at CVswitch = 0.40 which might require extreme adjustments in the range CVwR ~0.37 to 0.40.

**Author(s)**

H. Schütz

**References**

Tóthfalusi, L., Endrényi, L.
Sample Sizes for Designing Bioequivalence Studies for Highly Variable Drugs
free download
Wonnenmann, 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
Labes, D., Schütz, H., Fuglsang, A.
Perspectives on Scaled Average Bioequivalence Evaluation via Expanded Acceptance Limits (ABEL) and a Proposed Method to Control Type I Error
in preparation 2016

See Also
scABEL.ad, sampleN.scABEL, power.scABEL, scABEL

Examples

# Not run: due to timing policy of CRAN for examples
# may run ten seconds or more
# using all the defaults:
# partial replicate design, target power=80%,
# true assumed ratio = 0.90, 1E+6 simulated studies
# EMA regulatory settings (ABEL limits, PE constraint 0.8 - 1.25)
## Not run:
sampleN.scABEL.ad(CV = 0.3)
# should result in sample size n = 60, power = 0.8022
# Note: Without adjustment by sampleN.scABEL(): n = 54, power = 0.8159
## End(Not run)
# Easier to show the details:
## Not run:
sampleN.scABEL.ad(CV = 0.3, details = TRUE)
## End(Not run)
# # same with ANVISA settings, CVswitch = 40%
sampleN.scABEL.ad(CV = 0.3, regulator = "anvisa")
# should result in n = 60, power = 0.8101; no adjustment necessary
# # full replicate design, target power = 90%, pre-specified alpha 0.025
sampleN.scABEL.ad(CV = 0.3, targetpower = 0.8, design = "2x2x4", alpha.pre = 0.025)
# should result in n = 44, power = 0.8040; pre-specified alpha justified

---

sampleN.TOST  Sample size based on power of TOST

Description

Calculates the necessary sample size to have at least a given power.
**Usage**

```r
code

Usage

Usage

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.

 logscale 
 Should the data used on log-transformed or on original scale? TRUE or FALSE. 
 Defaults to TRUE.

 theta0 
 'True' or assumed bioequivalence ratio.
 In case of logscale=TRUE it must be given as ratio, otherwise as difference to 1. See examples.
 Defaults to 0.95 if logscale=TRUE or to 0.05 if logscale=FALSE.

 theta1 
 Lower bioequivalence limit.
 In case of logscale=TRUE it is given as ratio, otherwise as diff. to 1.
 Defaults to 0.8 if logscale=TRUE or to -0.2 if logscale=FALSE.

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

 CV 
 Coefficient of variation as ratio.

 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 chosen with method="owenq". 
 Another exact method via direct use of the bivariate non-central t-distribution 
 may be chosen with method="mvn". This may have somewhat lower precision 
 compared to Owen's Q and has 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 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 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.
\texttt{sampleN.TOST}

\begin{verbatim}
imax          Maximum number of steps in sample size search.
              Defaults to 100. Adaption only in rare cases needed.
\end{verbatim}

**Details**

The sample size is calculated 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.

**Value**

A dataframe 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 CV's f.i. use for-loops or the apply-family.

**Note**

Of course it is highly recommended to use the default method="exact" :)).
There is no reason beside testing and comparative purposes to use an approximation if the exact
method is available at no extra costs.

**Author(s)**

D. Labes

**References**

"Power of the Two One-Sided Tests Procedure in Bioequivalence"
J. of Pharmacokinetics and Biopharmaceutics, 18, 137-144.

"Sample Size Determination for Bioequivalence Assessment by Means of Confidence Intervals"
Int. J. of Clinical Pharmacology, Therapy and Toxicology, 29(1), 1-8 (1991)
30 Suppl.No.1, S51-58 (1992)

"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. of Clinical Pharmacology, Therapy and Toxicology, 30 Suppl.No.1, S59-62

Zhang P.
"A Simple Formula for Sample Size Calculation in Equivalence Studies"
scABEL

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, theta1=0.8)

scABEL

Helper function to calculate the (widened) scaled BE acceptance limits

Description

The (widened) scaled BE acceptance limits are calculated according to the regulatory settings of EMA, FDA, ANVISA or via user defined constants.

Usage

scABEL(CV, regulator = c("EMA", "ANVISA", "FDA", "USER"), r_const, CVswitch, CVcap)

Arguments

CV                  Coefficient of variation (of the Reference) as ratio
regulator           Regulatory body settings for the widening of the BE acceptance limits.
                    Defaults to regulator="EMA".
                    r_const             Regulatory constant for widening.
                    CVswitch           CV for switch to the widened ABEL.
                    CVcap              CV for cap of widening.
Details

r_const, CVswitch and CVcap must be given if regulator="USER". Otherwise these arguments may be missing.

Value

Returns a vector of length 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.

Author(s)

D. Labes

See Also

power.scABEL, sampleN.scABEL

Examples

```r
scABEL(CV=0.3, regulator="EMA")
# should give the usual limits:
# lower  upper
#  0.80  1.25
scABEL(CV=0.4, regulator="EMA")
# should give the widened limits:
# lower  upper
#  0.746177 1.340165
```

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

```r
scABEL.ad(alpha = 0.05, theta0, theta1, theta2, CV = 0.3,
          design = c("2x3x3", "2x2x4", "2x2x2"),
          regulator = c("EMA", "ANVISA"), n, alpha.pre = 0.05, imax=100,
          print = TRUE, details = FALSE, setseed = TRUE, nsims = 1e6)
```
Arguments

alpha  Type I error (TIE) probability (nominal level of the test). Per convention commonly set to 0.05. A lower value might be specified (e.g., in order to adjust for multiplicity in dose proportionality studies).

theta0 'True' or assumed bioavailability ratio. Defaults to 0.90 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  Coefficient(s) of variation as ratio (not percent). Defaults to 0.30 (i.e., the location of maximum inflation of the TIE for the EMA’s ABEL). If length(CV) = 1 the same CV of Test and Reference is assumed (CVwT = CVwR). If length(CV) = 2 the CV of Test must be given in CV[1] and the one of Reference in CV[2].

design  Design of the study to be planned. "2x3x3" is the partial replicate design (RRT|RTR|TRR). "2x2x3" is the 2-sequence 3-period full replicate design (RTR|TRT). "2x2x4" is the 2-sequence 4-period full replicate design (RTRTR|TRTR). Defaults to design = "2x3x3".

regulator  Regulatory body settings for the widening of the BE acceptance limits. Defaults to regulator = "EMA". This argument may be given also 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. If n is missing a sample size is estimated with targetpower = 0.5 and pre-specified alpha if defined. Else alpha is used.

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.

imax  Maximum number of steps in sample size search. Defaults to 100.

print  If TRUE (default), the function prints its results.

details  If TRUE, the relative change of the consumer risk 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.
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. Not recommended for CVwR >=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 a set.seed(123456) is issued if setseed=TRUE (default).

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. Examples of $U$ at the EMA’s CVswitch and CVcap:

```r
scABEL(CV=0.3, regulator="EMA")[["upper"]]
[1] 1.25
scABEL(CV=0.5, regulator="EMA")[["upper"]]
[1] 1.43191
```

Due to the symmetry around 1 results are valid for the lower (expanded) limit $L$ as well.

If a significant inflation of the TIE is expected (i.e., exceeding 0.05036 for one million simulations), alpha is iteratively adjusted until the consumer risk is maintained (n.s. > alpha0).

The significance limit is based on the one sided binomial test, e.g.,

```r
binom.test(0.05*1e6, 1e6, alternative="less", conf.level=1-0.05)$conf.int
```

Value

Returns a list with the input, adjusted alpha, and type I error (for nominal and adjusted alpha). If no adjustment is necessary, NA will be returned for adj. alpha and the TIE for alpha0 (or alpha1, if applicable) in TIE.unadj.

Warning

See the Warning section of the function `power.scABEL` concerning the power value agreement to those obtained from simulations via subject data.

Note

The type I error in ABEL depends only on CVwR and - to a minor degree - on the sample size. The TIE is assessed twice:

In the first step based on alpha (or alpha.pre) and compared to alpha. If no significant inflation is found, the algo stops.

Otherwise, alpha is iteratively adjusted (alway towards lower values) until no more inflation is detected. In the final assessment alpha.adj is compared to the nominal level of the test alpha.

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`.

In case of `regulator="ANVISA"` no official guidance exists. There is a discontinuity at `$CV_{switch} = 0.40$` which might require *extreme* adjustments in the range `$CV_{wR} \sim 0.37$ to $0.40$.

**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

Labes, D., Schütz, H., Fuglsang, A.
Perspectives on Scaled Average Bioequivalence Evaluation via Expanded Acceptance Limits (ABEL) and a Proposed Method to Control Type I Error
in preparation 2016

**See Also**

`sampleN.scABEL.ad`, `power.scABEL`, `scABEL`

**Examples**

```r
# partial replicate design, target power=80%,
# true assumed ratio = 0.90, 1E+6 simulated studies
# EMA regulatory settings (ABEL limits, PE constraint 0.8 - 1.25)
# Not run: due to timing policy of CRAN for examples
## Not run:
scABEL.ad(CV = 0.3)
## End(Not run)
# should result in adjusted alpha = 0.0339 (TIE 0.500, TIE for nominal alpha 0.0719)
#
# same with ANVISA settings, CVswitch=40%
scABEL.ad(CV = 0.3, regulator = "anvisa")
# no adjustment necessary (TIE 0.0503, n.s. > 0.05)
#
# EMA, full replicate design, CV 0.35, sample size 33 (unbalanced)
# Not run: due to timing policy of CRAN for examples
## Not run:
scABEL.ad(CV = 0.35, design = "2x2x4", n = c(16, 17))

## End(Not run)
# should result in adjusted alpha = 0.0363 (TIE 0.500, TIE for nominal alpha 0.0654)
```
type1error.2TOST

Type I error rate for two simultaneous TOST procedures

Description

Calculates the exact 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.

Usage

\[
type1error.2TOST(\alpha = c(0.05, 0.05), \text{logscale} = \text{TRUE}, \theta_1, \theta_2, \text{CV}, n, \rho, \text{design} = \text{"2x2"}, \text{robust} = \text{FALSE}, \text{setseed} = \text{TRUE}, \text{details} = \text{FALSE})
\]

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 or on original scale? TRUE or FALSE. Defaults to TRUE.
- **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 \(1/\theta_1\) if logscale=TRUE or as \(-\theta_1\) 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 parameters under consideration. This is defined as correlation between the estimator of the treatment difference of parameter one and the estimator of the treatment difference of parameter two.
- **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 \(n-\text{seq}\). See known_designs()$df2 for designs covered in this package. Has only effect for higher-order crossover designs.
**Details**

The exact calculations of the type 1 error rate are performed via integration of the 4-dimensional non-central t-distribution via function `pmvt()` of package `mvtnorm`. An absolute error tolerance of 1e-05 is set within `pmvt()`.

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 Type I Error rate if argument `details` = `FALSE`. A data.frame with the TIE for each of the eight null hypothesis regions if `details` = `TRUE`.

**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, CV must be of length two, thus further vectorizing is not possible.

Other vector input is not tested yet.

The calculation of the TIE may last some seconds. Be patient.

**Author(s)**

Benjamin Lang

**References**

Hua S. Y., Xu S., and D’Agostino Sr. R. B.  
"Multiplicity adjustments in testing for bioequivalence"  

"Letter to the Editor 'Comments on Multiplicity adjustments in testing for bioequivalence’".  
Statistics in Medicine.
See Also

`sampleN.2TOST`, `known.designs`

Examples

```r
## Not run:
# Replicate type I error rate for scenario S2 from Hua et al.
# runs 6-7 seconds, more than allowed for examples on CRAN
n <- 24
cv <- se2CV(c(0.0490 / sqrt(2/n), 0.0657 / sqrt(2/n)))
type1error.2TOST(CV = cv, n = n, rho = 0.6794, details = FALSE)
## End(Not run)
```
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