Package: Power2Stage (via r-universe)

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Title Power and Sample-Size Distribution of 2-Stage Bioequivalence Studies

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Description Contains functions to obtain the operational characteristics of bioequivalence studies in Two-Stage Designs (TSD) via simulations.

Imports PowerTOST, stats, mvtnorm, cubature

Suggests graphics

ByteCompile yes

URL https://github.com/Detlew/Power2Stage

BugReports https://github.com/Detlew/Power2Stage/issues

License GPL (>=2)

LazyLoad yes

Repository https://detlew.r-universe.dev

RemoteUrl https://github.com/detlew/power2stage

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Contents

`final.tsd.in` *Analysis after second stage of 2-stage 2x2 crossover design based on the Inverse Normal method*

Description

Following the design scheme according to `power.tsd.in` the function performs the analysis after the second stage has been performed.

Usage

```
final.tsd.in(alpha, weight, max.comb.test = TRUE, GMR1, CV1, n1, df1 = NULL,
             SEM1 = NULL, GMR2, CV2, n2, df2 = NULL, SEM2 = NULL,
             theta1, theta2)
```

Arguments

`alpha`	If one element is given, the overall one-sided significance level (not the adjusted level for stage 2). If two elements are given, the adjusted one-sided alpha levels for stage 1 and stage 2, respectively. If missing, defaults to `0.05`.
`weight`	Pre-defined weight(s) of stage 1. Note that using the notation from Maurer et al weight corresponds to information fraction, other literature may refer to sqrt(weight) as being the weight. `weight` must either contain one element (in case of `max.comb.test = FALSE`) or two elements (in case of `max.comb.test = TRUE`). If missing, defaults to `0.5` for `max.comb.test = FALSE` and to `c(0.5, 0.25)` for `max.comb.test = TRUE`.
`max.comb.test`	Logical; if `TRUE` (default) the maximum combination test will be used, otherwise the standard combination test.
`GMR1`	Observed ratio of geometric means (T/R) of stage 1 data (use *e.g.*, 0.95 for 95%).
`CV1`	Observed coefficient of variation of the intra-subject variability of stage 1 (use *e.g.*, 0.3 for 30%).
`n1`	Sample size of stage 1.
`df1`	Optional; Error degrees of freedom of stage 1 that can be specified in addition to `n1`.
`SEM1`	Optional; Standard error of the difference of means of stage 1 that can be specified in addition to `CV1`. Must be on additive scale (i.e. usually log-scale).

GMR2	Observed ratio of geometric means (T/R) of (only) stage 2 data (use *e.g.*, 0.95 for 95%).
CV2	Observed coefficient of variation of the intra-subject variability of (only) stage 2 (use *e.g.*, 0.3 for 30%).
n2	Sample size of stage 2.
df2	Optional; Error degrees of freedom of (only) stage 2 that can be specified in addition to n2.
SEM2	Optional; Standard error of the difference of means of (only) stage 2 that can be specified in addition to CV2. Must be on additive scale (i.e. usually log-scale).
theta1	Lower bioequivalence limit. Defaults to 0.8.
theta2	Upper bioequivalence limit. Defaults to 1.25.

Details

The observed values GMR1, CV1, n1 must be obtained using data from stage 1 only, and GMR2, CV2, n2 must be obtained using data from stage 2 only. This may be done via the usual ANOVA approach.

The optional arguments df1, SEM1, df2 and SEM2 require a somewhat advanced knowledge (provided in the raw output from for example the software SAS, or may be obtained via emmeans::emmeans). However, it has the advantage that if there were missing data the exact degrees of freedom and standard error of the difference can be used, the former possibly being non-integer valued (e.g. if the Kenward-Roger method was used).

Value

Returns an object of class "evaltsd" with all the input arguments and results as components. As part of the input arguments a component cval is also presented, containing the critical values for stage 1 and 2 according to the input based on alpha, weight and max.comb.test.
The class "evaltsd" has an S3 print method.

The results are in the components:

z1	Combination test statistic for first null hypothesis (standard combination test statistic in case of max.comb.test = FALSE or maximum combination test statistic in case of max.comb.test = TRUE)
z2	Combination test statistic for second null hypothesis (standard combination test statistic in case of max.comb.test = FALSE or maximum combination test statistic in case of max.comb.test = TRUE)
RCI	Repeated confidence interval for stage 2.
MEUE	Median unbiased point estimate as estimate for the final adjusted geometric mean ratio after stage 2.
stop_BE	Logical, indicating whether BE can be concluded after stage 2 or not.

Author(s)

B. Lang

References

König F, Wolfsegger M, Jaki T, Schütz H, Wassmer G.
Adaptive two-stage bioequivalence trials with early stopping and sample size re-estimation.
Vienna: 2014; 35^{th} Annual Conference of the International Society for Clinical Biostatistics. Poster P1.2.88
doi:10.13140/RG.2.1.5190.0967.

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Maurer W, Jones B, Chen Y. *Controlling the type 1 error rate in two-stage sequential designs when testing for average bioequivalence.*
Stat Med. 2018; 37(10): 1587–1607. doi:10.1002/sim.7614.

Wassmer G, Brannath W. *Group Sequential and Confirmatory Adaptive Designs in Clinical Trials.*
Springer 2016. doi:10.1007/9783319325620.

See Also

`power.tsd.in`, `interim.tsd.in`

Examples

```
# Example from Maurer et al.
final.tsd.in(GMR1 = exp(0.0424), CV1 = 0.3682, n1 = 20,
             GMR2 = exp(-0.0134), CV2 = 0.3644, n2 = 36)
# Example 2 from Potvin et al.
final.tsd.in(GMR1 = 1.0876, CV1 = 0.18213, n1 = 12,
             GMR2 = 0.9141, CV2 = 0.25618, n2 = 8)
```

`interim.tsd.in` *Interim analysis of first stage data of 2-stage 2x2 crossover designs based on the Inverse Normal method*

Description

Following the design scheme according to `power.tsd.in` the function performs the interim analysis of the first stage data.

Usage

```
interim.tsd.in(alpha, weight, max.comb.test = TRUE, targetpower = 0.8,
               GMR1, n1, CV1, df1 = NULL, SEM1 = NULL, theta1, theta2,
               GMR, usePE = FALSE, min.n2 = 4, max.n = Inf,
               fCpower = targetpower, fCrit = "CI", fClower, fCupper, fCNmax,
               ssr.conditional = c("error_power", "error", "no"),
               pmethod = c("exact", "nct", "shifted"))
```

Arguments

alpha	If one element is given, the overall one-sided significance level (not the adjusted level for stage 1). In this case the adjusted alpha levels will be calcualted internally. If two elements are given, the argument refers to the two adjusted one-sided alpha levels for stage 1 and stage 2, respectively. If missing, defaults to `0.05`.
weight	Pre-defined weight(s) of stage 1, see 'Details' for more information. Note that using the notation from Maurer et al, weight corresponds to information fraction, other literature may refer to sqrt(weight) as being the weight. `weight` must either contain one element (in case of `max.comb.test = FALSE`) or two elements (in case of `max.comb.test = TRUE`). If missing, defaults to `0.5` for `max.comb.test = FALSE` and to `c(0.5, 0.25)` for `max.comb.test = TRUE`.
max.comb.test	Logical; if `TRUE` (default) the maximum combination test will be used, otherwise the standard combination test.
targetpower	Desired (overall) target power to declare BE at the end of the trial.
GMR1	Observed ratio of geometric means (T/R) of stage 1 data (use *e.g.*, 0.95 for 95%).
n1	Sample size of stage 1.
CV1	Observed coefficient of variation of the intra-subject variability of stage 1 (use *e.g.*, 0.3 for 30%).
df1	Optional; Error degrees of freedom of stage 1 that can be specified in addition to `n1`.
SEM1	Optional; Standard error of the difference of means of stage 1 that can be specified in addition to `CV1`. Must be on additive scale (i.e. usually log-scale).
theta1	Lower bioequivalence limit. Defaults to 0.8.
theta2	Upper bioequivalence limit. Defaults to 1.25.
GMR	Assumed ratio of geometric means (T/R) to be used in power calculation for stage 1 and sample size re-estimation for stage 2.
usePE	If `TRUE` the sample size re-estimation is done with the observed point estimate (PE) of the treatment difference in stage 1. Defaults to `FALSE`. Note: The power of stage 1 used for the futility inspection and calculation of the estimated conditional target power is always calculated with the planning value `GMR`.
min.n2	Minimum sample size of stage 2. Defaults to 4. If the sample size re-estimation step gives a sample size for stage 2 less than `min.n2`, then `min.n2` will be used for stage 2.
max.n	Maximum overall sample size stage 1 + stage 2. This is *not* a futility criterion regarding the maximum sample size! If `max.n` is set to a finite value and the sample size re-estimation gives a sample size for stage 2 (`n2`) such that `n1 + n2 > max.n`, then the sample size for stage 2 will be set to `n2 = max.n - n1`. Defaults to `Inf`, *i.e.*, no constraint on the re-estimated sample size.

`fCpower` Threshold for power monitoring step to decide on futility for cases where BE has not been achieved after stage 1: If BE has not been achieved after stage 1 and the power for stage 1 is greater than or equal to `fCpower`, then the study will be considered a failure.

See 'Details' for more information on the choice of `fCpower`.

`fCrit` Futility criterion to use: `"No"` (no futility criterion regarding observed point estimate, confidence interval and maximum sample size), `"PE"` (observed point estimate of the geometric mean ratio from stage 1), `"CI"` (90% confidence interval of the geometric mean ratio from stage 1), `"Nmax"` (overall maximum sample size); or a combination thereof (concatenate abbreviations). Defaults to "CI".

`fClower` Lower futility limit for the PE or CI of stage 1.
If the PE or CI is completely outside of `fClower ... fCupper` the study is to be stopped due to futility (not BE).
May be missing. If `"PE"` or `"CI"` is specified within `fCrit`, the default will be set to 0.8 for `fCrit = "PE"` or 0.95 for `fCrit = "CI"`. If neither `"PE"` nor `"CI"` is specified within `fCrit`, there will be no futility constraint regarding point estimate or confidence interval from stage 1 (regardless of any specification of `fClower` and/or `fCupper`).

`fCupper` Upper futility limit for the PE or CI of stage 1.
Analogous to `fClower`: Will be set to `1/fClower` if missing.

`fCNmax` Futility criterion regarding maximum sample size. If the determined sample size for stage 2 (`n2`) is such that `n1 + n2 > fCNmax`, the study will not continue to stage 2 and stopped due to futility (not BE).
If `"Nmax"` is specified within `fCrit` and argument `fCNmax` is missing, the value will be set to `fCNmax = 4*n1`. If `"Nmax"` is not specified within `fCrit`, then there will be no futility constraint regarding maximum sample size (regardless of any specification of `fCNmax`).

`ssr.conditional`
Method for sample size re-estimation step: `"no"` does not use conditional error rates nor the estimated conditional target power for the second stage, `"error"` uses conditional error rates for the second stage, and `"error_power"` uses both conditional error rates and the estimated conditional target power for the second stage.
Defaults to `"error_power"`.

See also 'Details'.

`pmethod` Power calculation method, also to be used in the sample size estimation for stage 2.
Implemented are `"nct"` (approximate calculations via non-central *t*-distribution, `"exact"` (exact calculations via Owen's Q), and `"shifted"` (approximate calculation via shifted central *t*-distribution like in the paper of Potvin *et al.*)
In contrast to `power.tsd.in` the default value here is `"exact"`.

Details

The observed values of stage 1 (e.g. `GMR1`, `n1`, `CV1`) may be obtained based on the first stage data via the usual ANOVA approach.

The optional arguments df1 and SEM1 require a somewhat advanced knowledge (provided in the raw output from for example the software SAS, or may be obtained via emmeans::emmeans). However, it has the advantage that if there were missing data the exact degrees of freedom and standard error of the difference can be used, the former possibly being non-integer valued (e.g. if the Kenward-Roger method was used).

The weight argument always refers to the first weight of a pair of weights. For example, in case of max.comb.test = FALSE the standard combination test requires two weights (w, 1-w) but only the first one, w, is required as input argument here because the second weight is automatically specified once the first is given. Similarly for max.comb.test = TRUE, w and w* need to be specified, which in turn define the two pairs of weights (w, 1-w) and (w*, 1-w*).

If ssr.conditional = "error_power", the design scheme generally calculates the estimated conditional target power of the second stage and uses this value as desired target power in the sample size re-estimation process:
If fCpower > targetpower, then the conditional estimated target power may be negative. This does not seem sensible. Therefore, for such cases the desired target power for the sample size recalculation will be set to targetpower, i.e. ssr.conditional will be set to "error".
Also, if the futility criterion based on the power of stage 1 is met, then the conditional estimated target power will be negative. Thus, no further sample size calculation can be made. To acknowledge that this rule is nonbinding, for the purpose of calculating n2 the argument ssr.conditional is set to "error".

Value

Returns an object of class "evaltsd" with all the input arguments and results as components. As part of the input arguments a component cval is also presented, containing the critical values for stage 1 and 2 according to the input based on alpha, weight and max.comb.test.
The class "evaltsd" has an S3 print method.

The results are in the components:

p11	Observed p-value for first hypothesis.
p12	Observed p-value for second hypothesis.
z1	z statistic value for first null hypothesis.
z2	z statistic value for second null hypothesis.
RCI	Repeated confidence interval for stage 1. Corresponds to the usual CI with level alpha1.
MEUE	If the study stops, the median unbiased point estimate as estimate for the final adjusted geometric mean ratio after stage 1 (note that the value is identical to GMR1.)
futility	Three dimensional vector with either 0 or 1. The first component represents futility due to Power of first stage > fCpower, the second futility due to CI (or PE) outside of fClower ... fCupper, the third futility due to n1 + n2 > fCNmax. Note that the futility rules can be applied in a non-binding manner.
CI90	90% Confidence interval for observed ratio of geometric means from stage 1. If fCrit != "CI" result will be NULL.

`Power Stage 1`	Calculated power of stage 1.
`stop_s1`	Logical, indicating whether to stop after stage 1 (due to BE or due to futility).
`stop_fut`	Logical, indicating whether study is recommended to be stopped after stage 1 due to futility.
`stop_BE`	Logical, indicating whether BE could be concluded after stage 1 or not (regardless of any futility criterion).
`n2`	Required (total) sample size for stage 2 (will be zero if BE has been shown after stage 1).
`alpha_ssr`	Only applicable if BE has not been shown after stage 1. Contains alpha values for the two hypotheses required for sample size re-calculation. If `ssr.conditional = "no"` the result is equal to `alpha`, otherwise it contains the conditional error rates for the standard combination test (in case of `max.comb.test = FALSE`) or maximum combination test (in case of `max.comb.test = TRUE`).
`GMR_ssr`	Only applicable if BE has not been shown after stage 1. Contains the geometric mean ratio used for sample size re-calculation (accounts for adaptive planning step).
`targetpower_ssr`	Only applicable if BE has not been shown after stage 1. Contains the target power used for the sample size re-calculation (see also 'Details').

Author(s)

B. Lang

References

König F, Wolfsegger M, Jaki T, Schütz H, Wassmer G.
Adaptive two-stage bioequivalence trials with early stopping and sample size re-estimation.
Vienna: 2014; 35^{th} Annual Conference of the International Society for Clinical Biostatistics. Poster P1.2.88
doi:10.13140/RG.2.1.5190.0967.

Patterson SD, Jones B. *Bioequivalence and Statistics in Clinical Pharmacology.*
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Maurer W, Jones B, Chen Y. *Controlling the type 1 error rate in two-stage sequential designs when testing for average bioequivalence.*
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Wassmer G, Brannath W. *Group Sequential and Confirmatory Adaptive Designs in Clinical Trials.*
Springer 2016. doi:10.1007/9783319325620.

See Also

`power.tsd.in`, `final.tsd.in`

Examples

```
# Example from Maurer et al.
interim.tsd.in(GMR = 0.95, max.n = 4000,
               GMR1 = exp(0.0424), CV1 = 0.3682, n1 = 20)
# Example 2 from Potvin et al.
interim.tsd.in(GMR = 0.95, GMR1 = 1.0876, CV1 = 0.18213, n1 = 12,
               fCrit = "No", ssr.conditional = "no")
```

`power.tsd` *Power calculation of adaptive 2-stage BE studies in a 2x2 crossover design*

Description

This function calculates the 'empiric' power of 2-stage BE studies according to Potvin *et al.* via simulations. The Potvin methods are modified to include a futility criterion Nmax and to allow the sample size estimation step to be done with the point estimate (PE) and MSE (calculated from CV) of stage 1.

Usage

```
power.tsd(method = c("B", "C", "B0"), alpha0 = 0.05, alpha = c(0.0294, 0.0294),
          n1, GMR, CV, targetpower = 0.8, pmethod = c("nct", "exact", "shifted"),
           usePE = FALSE, Nmax = Inf, min.n2 = 0, theta0, theta1, theta2,
           npct = c(0.05, 0.5, 0.95), nsims, setseed = TRUE, details = FALSE)
```

Arguments

`method`	Decision schemes according to Potvin *et.al.* (defaults to `"B"`). Potvin's 'Method D' can be obtained by choosing `"C"` but setting `alpha=c(0.028, 0.028)`. Montague's 'Method D' can be obtained by choosing `"C"` but setting `alpha=c(0.028, 0.028)` and `GMR=0.9`. `method="B0"` uses the decision scheme of Zheng *et al.* MSDBE (modified sequential design for BE studies) which differs from B in case of different alphas w.r.t. power monitoring and BE decision in case of power >= target power.
`alpha0`	Alpha value for the first step(s) in Potvin `"C"`, the power inspection and BE decision if power > targetpower. Defaults to 0.05. Only observed if `method="C"`.

`alpha`	Vector (two elements) of the nominal alphas for the two stages. Defaults to Pocock's setting `alpha=c(0.0294, 0.0294)`.
	Common values together with other arguments are:
	`rep(0.0294, 2)`: Potvin *et al.* 'Method B'
	`rep(0.0269, 2)`: Fulgsang 'Method C/D' `(method="C", GMR=0.9, targetpower=0.9)`
	`rep(0.0274, 2)`: Fuglsang 'Method C/D' `(method="C", targetpower=0.9)`
	`rep(0.0280, 2)`: Montague *et al.* 'Method D' `(method="C", GMR=0.9)`
	`rep(0.0284, 2)`: Fulgsang 'Method B' `(GMR=0.9, targetpower=0.9)`
	`rep(0.0304, 2)`: Kieser & Rauch
	`c(0.01, 0.04)`: Zheng *et al.* 'MSDBE' `(method="B0")`

n1	Sample size of stage 1.
GMR	Ratio T/R to be used in decision scheme (power calculations in stage 1 and sample size estimation for stage 2).
CV	Coefficient of variation of the intra-subject variability (use *e.g.*, 0.3 for 30%).
targetpower	Power threshold in the power monitoring steps and power to achieve in the sample size estimation step.
pmethod	Power calculation method, also to be used in the sample size estimation for stage 2. Implemented are "nct" (approximate calculations via non-central *t*-distribution, "exact" (exact calculations via Owen's Q), and "shifted" (approximate calculation via shifted central *t*-distribution like in the paper of Potvin *et al.* Defaults to "nct" as a reasonable compromise between speed and accuracy in the sample size estimation step.
usePE	If TRUE the sample size estimation step is done with MSE **and** PE of stage 1. Defaults to FALSE *i.e.*, the sample size is estimated with GMR and MSE (calculated from CV) of stage 1 analogous to Potvin *et. al.* NB: The power inspection steps in the Potvin methods are always done with the GMR argument and MSE (CV) of stage 1.
Nmax	Futility criterion. If set to a finite value, all studies simulated in which a sample size >Nmax is obtained will be regarded as BE=FAIL. Set this argument to Inf, the default, to work without that futility criterion.
min.n2	Minimum sample size of stage 2. Defaults to zero. If the sample size estimation step gives N < n1+min.n2 the sample size for stage 2 will be forced to min.n2, *i.e.*, the total sample size to n1+min.n2.
theta0	True ratio of T/R for simulating. Defaults to the GMR argument if missing.
theta1	Lower bioequivalence limit. Defaults to 0.8.
theta2	Upper bioequivalence limit. Defaults to 1.25.
npct	Percentiles to be used for the presentation of the distribution of n(total)=n1+n2. Defaults to c(0.05, 0.5, 0.95) to obtain the 5% and 95% percentiles and the median.
nsims	Number of studies to simulate. If missing, nsims is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error ('alpha'), *i.e.*, with theta0 at the border or outside the acceptance range theta1 ... theta2.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(1234567) is issued if setseed=TRUE, the default. Set this argument to FALSE to view the variation in power between different runs.
details	If set to TRUE the function prints the results of time measurements of the simulation steps. Defaults to FALSE.

Details

The calculations follow in principle the simulations as described in Potvin *et al.*
The underlying subject data are assumed to be evaluated after log-transformation. But instead of

simulating subject data, the statistics pe1, mse1 and pe2, SS2 are simulated via their associated distributions (normal and χ^2 distributions).

Value

Returns an object of class `"pwrtsd"` with all the input arguments and results as components.
The class `"pwrtsd""` has an S3 print method.
The results are in the components:

`pBE`	Fraction of studies found BE.
`pBE_s1`	Fraction of studies found BE in stage 1.
`pct_s2`	Percentage of studies continuing to stage 2.
`nmean`	Mean of n(total), aka average total sample size (ASN).
`nrange`	Range (min, max) of n(total).
`nperc`	Vector of percentiles of the distribution of n(total).
`ntable`	Object of class `"table"` summarizing the discrete distribution of n(total) via its distinct values and counts of occurences of these values. This component is only given back if `usePE==FALSE` or otherwise if `is.finite(Nmax)`, *i.e.*, a futility criterion is used.

Author(s)

D. Labes

References

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA. *Sequential design approaches for bioequivalence studies with crossover designs.*
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Pharm Stat. 2015; 14(3):180–8. doi:10.1002/pst.1672

See Also

power.tsd.p for analogous calculations for 2-group parallel design.
power.tsd.fC for analogous calculations with futility check based on point estimate of stage 1.

Examples

```
# using all the defaults and 24 subjects in stage 1, CV of 25%
power.tsd(n1=24, CV=0.25)
# computation time ~ 1 sec
#
# as above, but save results for further use
res <- power.tsd(n1=24, CV=0.25)
## Not run:
# representation of the discrete distribution of n(total)
# via plot method of object with class "table" which creates a
# 'needle' plot
plot(res$ntable/sum(res$ntable), ylab="Density",
     xlab=expression("n"[total]), las=1,
     main=expression("Distribution of n"[total]))
#
# If you prefer a histogram instead (IMHO, not the preferred plot):
# reconstruct the ntotal values from the ntable
ntot <- rep.int(as.integer(names(res$ntable)),
                times=as.integer(res$ntable))
# annotated histogram
hist(ntot, freq=FALSE, breaks=res$nrange[2]-res$nrange[1],
     xlab=expression("n"[total]), las=1,
     main=expression("Histogram of n"[total]))
abline(v=c(res$nmean, res$nperc[["50%"]]), lty=c(1, 3))
legend("topright", box.lty=0, legend=c("mean", "median"),
       lty=c(1, 3), cex=0.9)
## End(Not run)
```

---

power.tsd.fC *Power calculation of adaptive 2-stage BE studies (2x2 crossover) with a futility criterion for the point estimate of T/R or its 90% CI*

Description

This function calculates the 'empiric' power of 2-stage BE studies according to Potvin *et al.* 'method B/C' via simulations. The Potvin methods are modified to include a futility criterion for the point estimate or for its 90%CI and to allow the sample size estimation step to be done with the point estimate (PE) and MSE of stage 1.

Usage

```
power.tsd.fC(method = c("B", "C", "B0"), alpha0 = 0.05, alpha = c(0.0294, 0.0294),
          n1, CV, GMR, targetpower = 0.8, pmethod = c("nct", "exact", "shifted"),
             usePE = FALSE, powerstep = TRUE, min.n2=0, max.n=Inf,
```

```
fCrit=c("CI", "PE"), fClower, fCupper, theta0, theta1, theta2,
npct = c(0.05, 0.5, 0.95), nsims, setseed = TRUE, details = FALSE)
```

Arguments

method	Decision schemes according to Potvin *et.al.* (defaults to "B"). Montague's 'Method D' can be obtained by choosing "C" but setting alpha=c(0.028, 0.028). 'Method E' of Xu *et al.* can be obtained by choosing "B" and setting alphas, futility criterion "CI", max.n, and n1 according to the reference. 'Method F' can be obtained choosing "C" with the appropriate design setting according to the reference. method="B0" uses the decision scheme of Zheng *et al.* MSDBE (modified sequential design for BE studies) which differs from B in case of different alphas w.r.t. power monitoring and BE decision in case of power >= target power.
alpha0	Alpha value for the first step(s) in Potvin "C", the power inspection and BE decision if power > targetpower. Defaults to 0.05. Only observed if method="C"
alpha	Vector (two elements) of the nominal alphas for the two stages. Defaults to Pocock's setting alpha=c(0.0294, 0.0294). Common values together with other arguments are: rep(0.0294, 2): Potvin *et al.* 'Method B' (fCrit="CI", fCupper=Inf) rep(0.0269, 2): Fulgsang 'Method C/D' (method="C", GMR=0.9, targetpower=0.9, fCrit="CI", rep(0.0274, 2): Fuglsang 'Method C/D' (method="C", targetpower=0.9, fCrit="CI", fCupper=I rep(0.0280, 2): Montague *et al.* 'Method D' (method="C", GMR=0.9, fCrit="CI", fCupper=Inf) rep(0.0284, 2): Fulgsang 'Method B' (GMR=0.9, targetpower=0.9, fCrit="CI", fCupper=Inf) rep(0.0304, 2): Kieser & Rauch (fCrit="CI", fCupper=Inf) c(0.01, 0.04): Zheng *et al.* 'MSDBE' (method="B0", fCrit="CI", fCupper=Inf) c(0.0249, 0.0357): Xu *et al.* 'Method E' for CV 10–30% (fCrit="CI", fClower=0.9374, max.n=42 c(0.0254, 0.0363): Xu *et al.* 'Method E' for CV 30–55% (fCrit="CI", fClower=0.9305, max.n=42 c(0.0248, 0.0364): Xu *et al.* 'Method F' for CV 10–30% (method="C", fCrit="CI", fClower=0.94 c(0.0259, 0.0349): Xu *et al.* 'Method F' for CV 30–55% (method="C", fCrit="CI", fClower=0.93
n1	Sample size of stage 1. For Xu's methods the recommended sample size should be at least 18 (if CV 10–30%) or 48 (if CV 30–55%).
CV	Coefficient of variation of the intra-subject variability (use *e.g.*, 0.3 for 30%).
GMR	Ratio T/R to be used in decision scheme (power calculations in stage 1 and sample size estimation for stage 2).
targetpower	Power threshold in the power monitoring steps and power to achieve in the sample size estimation step.
pmethod	Power calculation method, also to be used in the sample size estimation for stage 2. Implemented are "nct" (approximate calculations via non-central *t*-distribution, "exact" (exact calculations via Owen's Q), and "shifted" (approximate calculation via shifted central *t*-distribution like in the paper of Potvin *et al.* Defaults to "nct" as a reasonable compromise between speed and accuracy in the sample size estimation step.

usePE — If TRUE the sample size estimation step is done with MSE **and** PE of stage 1. Defaults to FALSE, *i.e.*, the sample size is estimated with anticipated (fixed) GMR given as argument and MSE of stage 1 (analogous to Potvin *et. al.*).

powerstep — If TRUE (the default) the interim power monitoring step in stage 1 evaluation of 'method B' will be done as described in Potvin *et.al.*
Setting this argument to FALSE will omit this step.
Has no effect if method="C" is choosen.

min.n2 — Minimum sample size of stage 2. Defaults to zero.
If the sample size estimation step gives N < n1+min.n2 the sample size for stage 2 will be forced to min.n2, *i.e.*, the total sample size to n1+min.n2.

max.n — If max.n is set to a finite value the re-estimated total sample size (N) is set to min(max.n, N).
Defaults to Inf which is equivalent to not constrain the re-estimated sample size.
Attention! max.n here is **not** a futility criterion like Nmax in other functions of this package.

fCrit — Futility criterion.
If set to "PE" the study stops after stage 1 if not BE and if the point estimate (PE) of stage 1 evaluation is outside the range defined in the next two arguments "fClower" and "fCupper".
If set to "CI" the study stops after stage 1 if not BE and if the confidence interval of stage 1 evaluation is outside the range defined in the next two arguments.
Defaults to "PE". Futility criterion to use for PE or CI.

fClower — Lower futility limit for the PE or CI of stage 1.
If the PE or CI is outside fClower ... fCupper the study is stopped in the interim with the result FAIL (not BE).
May be missing. Defaults then to 0.8 if fCrit="PE" or 0.925 if fCrit="CI".

fCupper — Upper futility limit for the PE or CI of stage 1.
Will be set to 1/fClower if missing.

theta0 — Assumed ratio of geometric means (T/R) for simulations. If missing, defaults to GMR.

theta1 — Lower bioequivalence limit. Defaults to 0.8.

theta2 — Upper bioequivalence limit. Defaults to 1.25.

npct — Percentiles to be used for the presentation of the distribution of n(total)=n1+n2. Defaults to c(0.05, 0.5, 0.95) to obtain the 5% and 95% percentiles and the median.

nsims — Number of studies to simulate.
If missing, nsims is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error ('alpha'), *i.e.*, with theta0 at the border or outside the acceptance range theta1 ... theta2.

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

details — If set to TRUE the function prints the results of time measurements of the simulation steps. Defaults to FALSE.

Details

The calculations follow in principle the simulations as described in Potvin *et al*.
The underlying subject data are assumed to be evaluated after log-transformation. But instead of simulating subject data, the statistics pe1, mse1 and pe2, SS2 are simulated via their associated distributions (normal and χ^2 distributions).

Value

Returns an object of class `"pwrtsd"` with all the input arguments and results as components.
The class `"pwrtsd"` has an S3 print method.
The results are in the components:

`pBE`	Fraction of studies found BE.
`pBE_s1`	Fraction of studies found BE in stage 1.
`pct_s2`	Percentage of studies continuing to stage 2.
`nmean`	Mean of n(total), aka average total sample size (ASN).
`nrange`	Range (min, max) of n(total).
`nperc`	Percentiles of the distribution of n(total).
`ntable`	Object of class `"table"` summarizing the discrete distribution of n(total) via its distinct values and counts of occurences of these values. This component is only given back if `usePE==FALSE` or `usePE==TRUE & fClower>0 & is.finite(fCupper)`, *i.e.*, a futility range is used.

Author(s)

D. Labes

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Pharm Stat. 2015; 14(3):180–8. doi:10.1002/pst.1672

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Pharm Stat. 2016;15(1):15–27. doi:10.1002/pst.1721

See Also

power.tsd

Examples

```
# using all the defaults
power.tsd.fC(CV=0.25, n1=24)
# run-time ~1 sec
## Not run:
# as above but storing the results
res <- power.tsd.fC(CV=0.25, n1=24)
# representation of the discrete distribution of n(total)
# via plot method of object with class "table" which creates a
# 'needle' plot
plot(res$ntable/sum(res$ntable), ylab="Density",
     xlab=expression("n"[total]), las=1,
     main=expression("Distribution of n"[total]))
## End(Not run)
```

---

power.tsd.GS *Power calculation for non-adaptive group sequential (2-stage) BE studies*

Description

This function calculates the 'empiric' power of group sequential 2-stage BE in 2×2 crossover designs via simulations.
The number of subjects in both stages has to be prespecified (non-adaptive).

Usage

```
power.tsd.GS(alpha = c(0.0294, 0.0294), n, CV, theta0, theta1, theta2,
             fCrit = c("CI", "PE"), fClower, fCupper, nsims, setseed = TRUE,
             details = FALSE)
```

Arguments

alpha	Vector of the two nominal alpha values to be used in the 100(1–2α) confidence interval calculations in the two stages. Use something like package ldbounds for choosing the nominal alphas.
n	Vector of the two sample sizes in stage 1 and stage 2. n(total) is n[1]+n[2] if a second stage is necessary. Otherwise it is n[1].
CV	Coefficient of variation of the intra-subject variability (use *e.g.*, 0.3 for 30%).
theta0	Assumed ratio of geometric means (T/R) for simulations. If missing, defaults to 0.95.
theta1	Lower bioequivalence limit. Defaults to 0.80.
theta2	Upper bioequivalence limit. Defaults to 1.25.

fCrit	Futility criterion. If set to "PE" the study stops after stage 1 if not BE and if the point estimate (PE) of stage 1 evaluation is outside the range defined in the next two arguments "fClower" and "fCupper". If set to "CI" the study stops after stage 1 if not BE and if the 90% confidence interval of stage 1 evaluation is outside the range defined in the next two arguments. Defaults to "CI".
fClower	Lower limit of the futility criterion. Defaults to 0 if missing, *i.e.*, no futility criterion.
fCupper	Upper limit of the futility criterion. Defaults to 1/fClower if missing.
nsims	Number of studies to simulate. If missing, nsims is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error ('alpha'), *i.e.*, with theta0 at the border or outside the acceptance range theta1 ... theta2.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(1234567) is issued if setseed=TRUE, the default. Set this argument to FALSE to view the variation in power between different runs.
details	If set to TRUE the function prints the results of time measurements of the simulation steps. Defaults to FALSE.

Details

The calculations follow in principle the simulations as described in Potvin *et al.* for adaptive designs, but with no interim power inspection and pre-specified (fixed) number of subjects in stage 2. The underlying subject data are assumed to be evaluated after log-transformation. But instead of simulating subject data, the statistics pe1, mse1 and pe2, SS2 are simulated via their associated distributions (normal and χ^2 distributions).

Value

Returns an object of class "pwrtsd" with all the input arguments and results as components.
The class "pwrtsd" has a S3 print method.
The results are in the components:

pBE	Fraction of studies found BE.
pBE_s1	Fraction of studies found BE in stage 1.
pct_s2	Percentage of studies continuing to stage 2.

Note

The code is reasonable fast. 1E6 sims take ~ 1 sec on my machine. Even 1E7 sims are meanwhile possible without too much beer. :-)

Author(s)

D. Labes

References

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Zheng Ch, Zhao L, Wang J. *Modifications of sequential designs in bioequivalence trials.* Pharm Stat. 2015; 14(3):180–8. doi:10.1002/pst.1672

See Also

`power.tsd` and `power.tsd.p` for adaptive sequential designs.

Examples

```
# using the Pocock alpha settings and no futility rule
# (defaults), a CV of 20% and 12 subjects in both stages,
# midway interim
power.tsd.GS(CV=0.2, n=c(12,12))
```

`power.tsd.in` *Power calculation of adaptive 2-stage BE studies with 2x2 crossover design, based on the Inverse Normal method*

Description

The function calculates the 'empirical' power of 2-stage BE studies based on the Inverse-Normal combination method. The main design scheme is according to Maurer *et al.* (Maximum Combination Test), but it may also be used for other/modified designs, e.g. standard combination method, usage of the observed treatment difference after stage 1 in the sample size re-estimation step or different futility criteria.

Usage

```
power.tsd.in(alpha, weight, max.comb.test = TRUE, n1, CV, targetpower = 0.8,
             theta0, theta1, theta2, GMR, usePE = FALSE, min.n2 = 4, max.n = Inf,
              fCpower = targetpower, fCrit = "CI", fClower, fCupper, fCNmax,
              ssr.conditional = c("error_power", "error", "no"),
              pmethod = c("nct", "exact", "shifted"), npct = c(0.05, 0.5, 0.95),
              nsims, setseed = TRUE, details = FALSE)
```

Arguments

alpha	If one element is given, the overall one-sided significance level. In this case the adjusted alpha levels will be calculated internally. If two elements are given, the argument refers to the two adjusted one-sided alpha levels for stage 1 and stage 2, respectively. If missing, defaults to 0.05.
weight	Pre-defined weight(s) of stage 1, see 'Details' for more information. Note that using the notation from Maurer et al, weight corresponds to information fraction, other literature may refer to sqrt(weight) as being the weight. weight must either contain one element (in case of max.comb.test = FALSE) or two elements (in case of max.comb.test = TRUE). If missing, defaults to 0.5 for max.comb.test = FALSE and to c(0.5, 0.25) for max.comb.test = TRUE.
max.comb.test	Logical; if TRUE (default) the maximum combination test will be used, otherwise the standard combination test.
n1	Sample size of stage 1.
CV	Coefficient of variation of the intra-subject variability (use *e.g.*, 0.3 for 30%).
targetpower	Desired (overall) target power to declare BE at the end of the trial.
theta0	Assumed ratio of geometric means (T/R) for simulations. If missing, defaults to GMR.
theta1	Lower bioequivalence limit. Defaults to 0.8.
theta2	Upper bioequivalence limit. Defaults to 1.25.
GMR	Assumed ratio of geometric means (T/R) to be used in power calculation for stage 1 and sample size re-estimation for stage 2. If missing, defaults to 0.95.
usePE	If TRUE the sample size re-estimation is done with the observed point estimate (PE) of the treatment difference in stage 1. Defaults to FALSE. Note: The power of stage 1 used for the futility inspection and calculation of the estimated conditional target power is always calculated with the the planning value GMR.
min.n2	Minimum sample size of stage 2. Defaults to 4. If the sample size re-estimation step gives a sample size for stage 2 less than min.n2, then min.n2 will be used for stage 2.
max.n	Maximum overall sample size stage 1 + stage 2. This is *not* a futility criterion regarding the maximum sample size! If max.n is set to a finite value and the sample size re-estimation gives a sample size for stage 2 (n2) such that n1 + n2 > max.n, then the sample size for stage 2 will be set to n2 = max.n - n1. Defaults to Inf, *i.e.*, no constraint on the re-estimated sample size.
fCpower	Threshold for power monitoring step to decide on futility for cases where BE has not been achieved after stage 1: If BE has not been achieved after stage 1 and the power for stage 1 is greater than or equal to fCpower, then the study will be considered a failure. See 'Details' for more information on the choice of fCpower.

`fCrit` Futility criterion to use: `"No"` (no futility criterion regarding observed point estimate, confidence interval and maximum sample size), `"PE"` (observed point estimate of the geometric mean ratio from stage 1), `"CI"` (90% confidence interval of the geometric mean ratio from stage 1), `"Nmax"` (overall maximum sample size); or a combination thereof (concatenate abbreviations; see 'Examples'). Defaults to "CI".

`fClower` Lower futility limit for the PE or CI of stage 1.
If the PE or CI is completely outside of `fClower` ... `fCupper` the study is stopped due to futility (not BE).
May be missing. If `"PE"` or `"CI"` is specified within `fCrit`, the default will be set to 0.8 for `fCrit = "PE"` or 0.95 for `fCrit = "CI"`. If neither `"PE"` nor `"CI"` is specified within `fCrit`, there will be no futility constraint regarding point estimate or confidence interval from stage 1 (regardless of any specification of `fClower` and/or `fCupper`).

`fCupper` Upper futility limit for the PE or CI of stage 1.
Analogous to `fClower`: Will be set to `1/fClower` if missing.

`fCNmax` Futility criterion regarding maximum sample size. If the determined sample size for stage 2 (`n2`) is such that `n1 + n2 > fCNmax`, the study will not continue to stage 2 and stopped due to futility (not BE).
If `"Nmax"` is specified within `fCrit` and argument `fCNmax` is missing, the value will be set to `fCNmax = 4*n1`. If `"Nmax"` is not specified within `fCrit`, then there will be no futility constraint regarding maximum sample size (regardless of any specification of `fCNmax`).

`ssr.conditional`
Method for sample size re-estimation step: `"no"` does not use conditional error rates nor the estimated conditional target power for the second stage, `"error"` uses conditional error rates for the second stage, and `"error_power"` uses both conditional error rates and the estimated conditional target power for the second stage.
Defaults to `"error_power"`.

See also 'Details'.

`pmethod` Power calculation method, also to be used in the sample size estimation for stage 2.
Implemented are `"nct"` (approximate calculations via non-central *t*-distribution, `"exact"` (exact calculations via Owen's Q), and `"shifted"` (approximate calculation via shifted central *t*-distribution like in the paper of Potvin *et al.*)
Defaults to `"nct"` as it is a reasonable compromise between speed and accuracy in the sample size estimation step.

`npct` Percentiles to be used for the presentation of the distribution of `n(total)=n1+n2`.
Defaults to `c(0.05, 0.5, 0.95)` to obtain the 5% and 95% percentiles and the median.

`nsims` Number of studies to simulate.
If missing, `nsims` is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error (`'alpha'`), *i.e.*, with `theta0` at the border of the acceptance range `theta1` ... `theta2`.

setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(1234567) is issued if setseed=TRUE, the default. Set this argument to FALSE to view the variation in power between different runs.
details	If set to TRUE the function prints the results of time measurements of the simulation steps. Default to FALSE.

Details

The underlying subject data are assumed to be evaluated after log-transformation. But instead of simulating subject data, the statistics pe1, mse1 and pe2, mse2 are simulated via their associated distributions (Normal and χ^2 distribution).

The weight argument always refers to the first weight of a pair of weights. For example, in case of max.comb.test = FALSE the standard combination test requires two weights (w, 1-w) but only the first one, w, is required as input argument here because the second weight is automatically specified once the first is given. Similarly for max.comb.test = TRUE, w and w* need to be specified, which in turn define the two pairs of weights (w, 1-w) and (w*, 1-w*).

If ssr.conditional = "error_power", the design scheme generally calculates the estimated conditional target power of the second stage and uses this value as desired target power in the sample size re-estimation process:
If fCpower > targetpower, then the conditional estimated target power may be negative. This does not seem sensible. Therefore, for such cases the desired target power for the sample size re-calculation will be set to targetpower, i.e. ssr.conditional will be set to "error".

Value

Returns an object of class "pwrtsd" with all the input arguments and results as components. As part of the input arguments a component cval is also presented, containing the critical values for stage 1 and 2 according to the input based on alpha, weight and max.comb.test.
The class "pwrtsd" has an S3 print method.

The results are in the components:

pBE	Fraction of studies found BE.
pBE_s1	Fraction of studies found BE in stage 1.
pct_stop_s1	Percentage of studies stopped after stage 1 (due to BE or due to futility).
pct_stop_fut	Percentage of studies stopped after stage 1 due to futility.
pct_s2	Percentage of studies continuing to stage 2.
nmean	Mean of n(total).
nrange	Range (min, max) of n(total).
nperc	Vector of percentiles of the distribution of n(total).

Author(s)

B. Lang

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See Also

`interim.tsd.in`, `final.tsd.in`

Examples

```
# 12 subjects in stage 1, CV of 20%, no futility rule, otherwise all defaults
# except too low number of sims due to CRAN policy for run-time of examples
# This setting resembles values in Table 6.8 and 6.10 in Patterson and Jones
# if nsims=1e5 (default)
power.tsd.in(n1 = 12, CV = 0.2, fCrit = "No", nsims=1e4)

# Note that actual replication would require the following additional
# arguments (extremely long run-time)
## Not run:
power.tsd.in(n1 = 12, CV = 0.2, fCrit = "No", max.n = 4000,
             pmethod = "exact", nsims = 1E6)
## End(Not run)

# Table 8 in Maurer et al
power.tsd.in(n1 = 36, CV = 0.4, max.n = 4000)

# Same example as before but with additional futility criterion regarding
# maximum sample size (using the default 4*n1 as maximum bound)
power.tsd.in(n1 = 36, CV = 0.4, max.n = 4000, fCrit = c("CI", "Nmax"))
```

`power.tsd.KM` *Power calculation of adaptive 2-stage BE studies (2x2 crossover) (variant of power.2stage to obtain the results of Karalis / Macheras)*

Description

This function calculates the 'empiric' power of 2-stage BE studies according to Potvin *et al.* via simulations. The Potvin methods are modified as described by Karalis & Macheras to include a futility criterion Nmax and to perform the power calculation steps and the sample size estimation step in the decision schemes with the MSE (calculated from CV) **and** the point estimate (PE) of T/R from stage 1.

Usage

```
power.tsd.KM(method = c("C", "B"), alpha0 = 0.05, alpha = c(0.0294, 0.0294),
             n1, CV, targetpower = 0.8, pmethod = c("nct", "exact"),
             Nmax = 150, theta0, theta1, theta2, npct = c(0.05, 0.5, 0.95),
             nsims, setseed = TRUE, details = FALSE)
```

Arguments

`method`	Decision schemes according to Potvin *et al.* Default is `"C"` aka TSD in the paper of Karalis & Macheras if setting `alpha=c(0.0294, 0.0294)`. TSD-1 of Karalis can be obtained by choosing `"C"` but setting `alpha=c(0.028, 0.028)`. TSD-2 of Karalis can be obtained by choosing `"B"` and setting `alpha=c(0.0294, 0.0294)`.
`alpha0`	Alpha value for the first step(s) in Potvin C aka TSD of Karalis & Macheras or TSD-1 of Karalis, the power inspection and BE decision if power > targetpower. Defaults to 0.05.
`alpha`	Vector (two elements) of the nominal alphas for the two stages. Defaults to Pocock's alpha setting `alpha=c(0.0294, 0.0294)` as in TSD of Karalis & Macheras.
`n1`	Sample size of stage 1.
`CV`	Coefficient of variation of the intra-subject variability (use *e.g.*, 0.3 for 30%).
`targetpower`	Power threshold in the first step of Potvin `"C"` and power to achieve in the sample size estimation step.
`pmethod`	Power calculation method, also to be used in the sample size estimation for stage 2. Implemented are `""nct"` (approximate calculations via non-central *t*-distribution and `"exact"` (exact calculations via Owen's Q). Defaults to `"nct"` as a reasonable compromise between speed and accuracy in the sample size estimation step.
`Nmax`	Futility criterion. If set to a finite value all studies simulated in which a sample size >Nmax is obtained will be regarded as BE=FAIL. Defaults to 150, as recommended by Karalis & Macheras. Set this argument to `Inf`, to work without that futility criterion.
`theta0`	Assumed ratio of geometric means (T/R) for simulations. If missing, defaults to GMR.
`theta1`	Lower bioequivalence limit. Defaults to 0.8.
`theta2`	Upper bioequivalence limit. Defaults to 1.25.

npct	Percentiles to be used for the presentation of the distribution of n(total)=n1+n2. Defaults to c(0.05, 0.5, 0.95) to obtain the 5% and 95% percentiles and the median.
nsims	Number of studies to simulate. If missing, nsims is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error ('alpha'), *i.e.*, with theta0 at the border or outside the acceptance range theta1 ... theta2.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(1234567) is issued if setseed=TRUE, the default. Set this argument to FALSE to view the variation in power between different runs.
details	If set to TRUE the function prints the results of time measurements of the simulation steps. Defaults to FALSE.

Details

The calculations follow in principle the simulations as described in Potvin *et al*.
The underlying subject data are assumed to be evaluated after log-transformation. But instead of simulating subject data, the statistics pe1, mse1 and pe2, SS2 are simulated via their associated distributions (normal and χ^2 distributions).

In contrast to Potvin *et al.* the power calculation steps as well as the sample size adaption step of the decision schemes are done using the MSE (calculated from CV) **and** the point estimate from stage 1.
This resembles the methods described in Karalis & Macheras and Karalis.

Value

Returns an object of class "pwrtsd" with all the input arguments and results as components.
The class "pwrtsd" has a S3 print method.
The results are in the components:

pBE	Fraction of studies found BE.
pBE_s1	Fraction of studies found BE in stage 1.
pct_s2	Percentage of studies continuing to stage 2.
nmean	Mean of n(total).
nrange	Range (min, max) of n(total).
nperc	Percentiles of the distribution of n(total).
ntable	Object of class "table" summarizing the discrete distribution of n(total) via its distinct values and counts of occurences of these values. This component is only given back if is.finite(Nmax).

Author(s)

D. Labes

References

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA. *Sequential design approaches for bioequivalence studies with crossover designs.*
Pharm Stat. 2008; 7(4):245–62. doi:10.1002/pst.294

Karalis V, Macheras P. *An Insight into the Properties of a Two-Stage Design in Bioequivalence Studies.*
Pharm Res. 2013; 30(7):1824–35. doi:10.1007/s1109501310263

Karalis V. *The role of the upper sample size limit in two-stage bioequivalence designs.*
Int J Pharm. 2013; 456(1):87–94. doi:10.1016/j.ijpharm.2013.08.013

Fuglsang A. *Futility Rules in Bioequivalence Trials with Sequential Designs.*
AAPS J. 2014; 16(1):79–82. doi:10.1208/s1224801395400

Schütz H. *Two-stage designs in bioequivalence trials.*
Eur J Clin Pharmacol. 2015; 71(3):271–81. doi:10.1007/s0022801518062

Examples

```
# using all the defaults
# but too low number of sims to complain with the CRAN policy:
# "check time only a few seconds per example"
# minimum number of sims should be 1E5 for power, 1E6 sims for 'alpha'
power.tsd.KM(n1=16, CV=0.2, nsims=1E4)
# ~3 sec if nsims=1E5
```

`power.tsd.p` *Power calculation of adaptive 2-stage BE studies in 2-group parallel designs*

Description

This functions calculate the 'empirical' power of 2-stage BE studies with 2 parallel groups according to Fuglsang 2014 via simulations. The Potvin decision schemes are modified to include a futility criterion Nmax, a minimum number of subjects to be included in stage 2 and to allow the sample size estimation step to be done with point estimate and variabilities from stage 1 (fully adaptive).

Function `power.tsd.pAF()` performes exactly as described in Fuglsang's paper, namely the power monitoring steps and the sample size estimation are based always on the pooled *t*-test.

Function `power.tsd.p()` with argument `test="welch"` on the other hand uses the genuine power of Welch's test. Moreover it accepts unequal treatment groups in stage 1.

Usage

```
power.tsd.p(method = c("B", "C"), alpha0 = 0.05, alpha = c(0.0294, 0.0294),
          n1, GMR, CV, targetpower = 0.8, pmethod = c("nct", "exact", "shifted"),
        usePE = FALSE, Nmax = Inf, min.n2=0, test = c("welch", "t-test", "anova"),
           theta0, theta1, theta2, npct = c(0.05, 0.5, 0.95), nsims,
```

```
            setseed = TRUE, details = FALSE)

power.tsd.pAF(method = c("B", "C"), alpha0 = 0.05, alpha = c(0.0294, 0.0294),
          n1, GMR, CV, targetpower = 0.8, pmethod = c("shifted", "nct", "exact"),
              usePE = FALSE, Nmax = Inf, test = c("welch", "t-test", "anova"),
              theta0, theta1, theta2, npct = c(0.05, 0.5, 0.95), nsims,
              setseed = TRUE, details = FALSE)
```

Arguments

method	Decision schemes according to Potvin *et.al.* (defaults to "B"). Potvin's 'method D' can be obtained by choosing "C" but setting alpha=c(0.028, 0.028).
alpha0	Alpha value for the first step(s) in Potvin "C", the power inspection and BE decision if power > targetpower. Defaults to 0.05.
alpha	Vector (two elements) of the nominal alphas for the two stages. Defaults to Pocock's alpha setting alpha=c(0.0294, 0.0294).
n1	Sample size of stage 1. Function power.tsd.p() accepts also a vector of stage 1 sample sizes with two elements, where the number of subjects in the in treatment group *T* should be given in the first element and the number of subjects in the treatment group *R* in the second. If given with one element, the total n1 should be even.
GMR	Ratio T/R to be used in decision scheme (power calculations in stage 1 and sample size estimation for stage 2).
CV	Coefficient of variation of the total variability (use *e.g.*, 0.3 for 30%) Can be a vector with two elements. In that case CV[1] is for the group under the Test treatment and CV[2] for the group under the Reference.
targetpower	Power threshold in the power monitoring steps and power to achieve in the sample size estimation step.
pmethod	Power calculation method, also to be used in the sample size estimation for stage 2. Implemented are "nct" (approximate calculations via non-central *t*-distribution, "exact" (exact calculations via Owen's Q), and "shifted" (approximate calculation via shifted central *t*-distribution Defaults to "nct" for speed reasons in function power.tsd.p() as a reasonable compromise between speed and accuracy in the sample size estimation step. Defaults to "shifted" in function power.tsd.pAF() for consistancy with Fuglsang.
usePE	If TRUE the sample size estimation step is done with MSE **and** PE of stage 1. Defaults to FALSE *i.e.*, the sample size is estimated with GMR and MSE (calculated from CV) of stage 1 analogous to Potvin *et. al.* NB: The power inspection steps in the Potvin methods are always done with the GMR argument and MSE (CV) of stage 1.
Nmax	Futility criterion. If set to a finite value, all studies simulated in which a sample size >Nmax is obtained will be regarded as BE=FAIL. Set this argument to Inf, the default, to work without that futility criterion.

`min.n2` Minimum sample size of stage 2.
If the sample size estimation step gives `N < n1+min.n2` the sample size for stage 2 will be forced to `min.n2`, *i.e.* the total sample size to `n1+min.n2`.
Defaults to zero, *i.e.*, no minimum sample size for stage 2 is applied.

`test` Test on which the CI calculations are based on.
Defaults to `"welch"` = Welch's *t*-test accounting for heteroscedasticity in the variabilities of Test and Reference, but neglecting stage effects.
`"anova"` calculates the 100(1–2α) confidence interval based on an ANOVA with treatment and stage in the model.
`"t-test"` calculates the 100(1–2α) confidence interval based on the *t*-test assuming equal variabilities of Test and Reference and neglecting stage effects.

`theta0` Assumed ratio of geometric means (T/R) for simulations. If missing, defaults to `GMR`.

`theta1` Lower bioequivalence limit. Defaults to 0.8.

`theta2` Upper bioequivalence limit. Defaults to 1.25.

`npct` Percentiles to be used for the presentation of the distribution of `n(total)=n1+n2`.
Defaults to `c(0.05, 0.5, 0.95)` to obtain the 5% and 95% percentiles and the median.

`nsims` Number of studies to simulate.
If missing, `nsims` is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error (`'alpha'`), *i.e.*, with `theta0` at the border or outside the acceptance range `theta1 ... theta2`.

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

`details` If set to `TRUE` the function prints the results of time measurements of the simulation steps. Defaults to `FALSE`.

Details

The calculations follow in principle the simulations as described by Fuglsang.
The underlying subject data are assumed to be evaluated after log-transformation. But instead of simulating subject data the statistics (mean and variance of Test and Reference of stage 1 and stage 2) are simulated via their associated distributions (normal and χ^2).

Value

Returns an object of class `"pwrtsd"` with all the input arguments and results as components.
The class `"pwrtsd"` has an S3 print method.
The results are in the components:

`pBE` Fraction of studies found BE.

`pBE_s1` Fraction of studies found BE in stage 1.

`pct_s2` Percentage of studies continuing to stage 2.

nmean	Mean of n(total).
nrange	Range (min, max) of n(total).
nperc	Percentiles of the distribution of n(total).
ntable	Object of class "table" summarizing the discrete distribution of n(total) via its distinct values and counts of occurences of these values. This component is only given back if usePE==FALSE or otherwise if is.finite(Nmax), *i.e.*, a futility criterion is used.

Author(s)

D. Labes

References

Fuglsang A. *Sequential Bioequivalence Approaches for Parallel Design.*
AAPS J. 2014; 16(3):373–8. doi:10.1208/s1224801495711

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA. *Sequential design approaches for bioequivalence studies with crossover designs.*
Pharm Stat. 2008; 7(4):245–62. doi:10.1002/pst.294

See Also

power.2stage for analogous calculations for the 2×2 crossover.

Examples

```
# using all the defaults
power.tsd.p(n1=48, CV=0.25)
```

---

power.tsd.ssr *Power of 2-stage BE studies in 2x2 crossover designs with interim sample size re-estimation*

Description

This function calculates the 'empiric' power (via simulations) of 2-stage BE studies with interim sample size re-estimation (*i.e.*, but no BE decision after stage 1). The sample size re-estimation can be done blinded or unblinded.

Usage

```
power.tsd.ssr(alpha = 0.05, n1, GMR, CV, targetpower = 0.8,
              pmethod = c("nct", "exact", "shifted", "ls"), blind = FALSE,
              usePE = FALSE, min.n = 0, max.n = Inf, theta0, theta1, theta2,
             npct = c(0.05, 0.5, 0.95), nsims, setseed = TRUE, details = FALSE)
```

Arguments

alpha	Nominal type I error. Has to be adjusted in case of inflation of the Type I Error.
n1	Sample size of stage 1.
GMR	Ratio T/R to be used in the sample size re-estimation. Defaults to 0.95 if missing.
CV	Coefficient of variation of the intra-subject variability (use *e.g.*, 0.3 for 30%). Anticipated population value.
targetpower	Power to achieve in the sample size estimation step.
pmethod	Power calculation method to be used in the sample size re-estimation for stage 2. Implemented are "nct" (approximate calculations via non-central *t*-distribution, "exact" (exact calculations via Owen's Q), and "shifted" (approximate calculation via shifted central *t*-distribution. Also implemented is the large sample approximation as used in the references. Defaults to "nct" as a reasonable compromise between speed and accuracy in the sample size estimation step.
blind	If TRUE the blinded estimate of the intra-subject variance, *i.e.*, the estimate from the period differences, is used in sample size estimation. If FALSE the usual MSE from stage 1 is used. Defaults to FALSE since most BE studies are open.
usePE	If TRUE the point estimate from the interim analysis is used in the sample size re-estimation. Defaults to FALSE. usePE = TRUE doesn't make sense if blind = TRUE. In that case the function issues a warning and usePE is reset to usePE = FALSE.
min.n	If min.n>n1, the re-estimated sample size (N) is set to max(min.n,N). If min.n=0 (the default), no minimal sample size is applied.
max.n	If max.n is set to a finite value the re-estimated sample size (N) is set to min(max.n,N). Defaults to Inf which is equivalent to not constrain the re-estimated sample size. Attention! max.n is here **not** a futility criterion like Nmax in other functions of this package.
theta0	Assumed ratio of geometric means (T/R) for simulations. If missing, defaults to GMR.
theta1	Lower bioequivalence limit. Defaults to 0.8.
theta2	Upper bioequivalence limit. Defaults to 1.25.
npct	Percentiles to be used for the presentation of the distribution of n(total)=n1+n2. Defaults to c(0.05, 0.5, 0.95) to obtain the 5% and 95% percentiles and the median.
nsims	Number of studies to simulate. If missing, nsims is set to 1E+05 = 100,000 or to 1E+06 = 1 Mio if estimating the empiric Type I Error ('alpha'), *i.e.*, with theta0 at the border or outside the acceptance range theta1 ... theta2.
setseed	Simulations are dependent on the starting point of the (pseudo) random number generator. To avoid differences in power for different runs a set.seed(1234567) is issued if setseed=TRUE, the default. Set this argument to FALSE to view the variation in power between different runs.

`details` If set to `TRUE` the function prints the results of time measurements of the simulation steps. Defaults to `FALSE`.

Details

The calculations follow in principle the simulations as described in Potvin *et al*.
The underlying subject data are assumed to be evaluated after log-transformation. But instead of simulating subject data, the statistics pe1, mse1 and pe2, SS2 are simulated via their associated distributions (normal and χ^2 distributions).

Value

Returns an object of class class `"pwrtsd"` with all the input arguments and results as components.
The class class `"pwrtsd"` has a S3 print method.
The results are in the components:

`pBE`	Fraction of studies found BE.
`pct_s2`	Percentage of studies continuing to stage 2.
`nmean`	Mean of n(total).
`nrange`	Range (min, max) of n(total).
`nperc`	Percentiles of the distribution of n(total).
`ntable`	Object of class `"table"` summarizing the discrete distribution of n(total) via its unique values and counts of occurences of these values. ntable is only given back if `usePE = FALSE`

Note

The computation time is in the magnitude of a few seconds for 100,000 sim's on my machine (Intel core i7 2.5 GHz, 12GB RAM) if the non-central *t* approximation is used. Thus be a bit patient if you simulate for the Tpye I Error 'alpha' with 1 Mio sim's.
Using the crude `pmethod="ls"` on the other hand results in a nearly immediate sample size re-estimation.

Author(s)

D. Labes

References

Golkowski D, Friede T, Kieser M. *Blinded sample size re-estimation in crossover bioequivalence trials.*
Pharm Stat. 2014; 13(3):157–62. doi:10.1002/pst.1617

Jones B, Kenward MG. *Design and Analysis of Cross-Over Trials.*
Boca Raton: CRC Press; 3^{rd} edition 2014. Chapter 12.

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA. *Sequential design approaches for bioequivalence studies with crossover designs.*
Pharm Stat. 2008; 7(4):245–62. doi:10.1002/pst.294

See Also

power.tsd for 2-stage studies with interim BE decision.

Examples

```
# Not run to comply with CRAN policy about examples' run-time;
# minimum number of sim's should be 1E5 for 'power', 1E6 sim's for 'alpha'
## Not run:
power.tsd.ssr(alpha=0.05, n1=10, GMR=1, CV=0.239, targetpower=0.9,
              pmethod="ls", blind=TRUE, theta0=1.25)
# should give an alpha-inflation 0.072359 (run time <5 seconds)
# repeated with noncentral t-approximation
power.tsd.ssr(alpha=0.05, n1=10, GMR=1, CV=0.239, targetpower=0.9,
              pmethod="nct", blind=TRUE, theta0=1.25)
# should give an alpha-inflation 0.069789 (run time ~20 seconds)
#
# adjusted alpha to control the Type I Error, noncentral t-approx.
power.tsd.ssr(alpha=0.03505, n1=10, GMR=1, CV=0.239, targetpower=0.9,
              pmethod="nct", blind=TRUE, theta0=1.25)
# should control the TIE with 0.049877
## End(Not run)
```

---

sampleN2.TOST *Sample size re-estimation of adaptive 2-stage BE studies in 2x2 crossover and parallel designs based on power of TOST*

Description

This function estimates the necessary sample size of stage 2 to have at least a given power.

Usage

```
sampleN2.TOST(alpha = 0.0294, CV, n1, theta0 = 0.95,
              theta1 = 0.8, theta2 = 1.25, targetpower = 0.8,
              design = "2x2", method = "exact", imax = 100)
```

Arguments

alpha	Alpha value for the final analysis of pooled data. Defaults to Pocock's alpha setting alpha=0.0294.
CV	Coefficient of variation of the intra-subject variability as ratio.
n1	Sample size of stage 1.
theta0	True ratio of T/R for simulating. Defaults to 0.95 argument if missing.
theta1	Lower bioequivalence limit. Defaults to 0.8.
theta2	Upper bioequivalence limit. Defaults to 1.25.
targetpower	Power to achieve at least. Must be >0 and <1.

design	Character string describing the study design. Implemented are "2x2" and "parallel".
method	Method for calculation of the power. Implemented are "exact" (exact calculation via Owen's Q), "nct" (approximate calculation via non-central *t*-distribution, and "shifted" (approximate calculation via shifted central *t*-distribution like in the paper of Potvin *et al.* Defaults to "exact".
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 of the TOST procedure.
Start value for the sample size search is taken from a large sample approximation according to Zhang, modified.

Value

A data.frame with the input and results will be returned.
The "Sample size" column contains the sample size for the second stage.

Note

Since in the final analysis one degree of freedom less than in a fixed sample design (or in stage 1) is used, power will be slightly lower than the one obtained with function sampleN.TOST of package PowerTOST. However, different *sample sizes* are extremely unlikely.

Author(s)

H. Schütz, D. Labes

References

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DJ, Smith RA.
Sequential design approaches for bioequivalence studies with crossover designs.
Pharm Stat. 2008; 7(4):245–62. doi:10.1002/pst.294

Zhang P. *A Simple Formula for Sample Size Calculation in Equivalence Studies.*
J Biopharm Stat. 2003; 13(3):529–38. doi:10.1081/BIP120022772

Examples

```
# using all the defaults, CV of 25% and 12 subjects in stage 1
print(sampleN2.TOST(CV=0.25, n1=12), row.names=FALSE)
# should give a stage 2 sample size of 22 and achieved power ~0.812
# CV 10% and 12 subjects in stage 1
print(sampleN2.TOST(CV=0.1, n1=12), row.names=FALSE)
# should give a sample size of 0 (second stage not reasonable
# since power ~0.973 was already achieved in stage 1)
```

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