

Package ‘asd’

October 12, 2022

Type Package

Title Simulations for Adaptive Seamless Designs

Version 2.2

Date 2016-05-23

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Depends mvtnorm

Description Package runs simulations for adaptive seamless designs with and without early outcomes for treatment selection and subpopulation type designs.

License GPL-3

NeedsCompilation no

Repository CRAN

Date/Publication 2016-05-23 10:14:13

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Description

Functions to run simulations for trial designs that either (i) test a number of experimental treatments against a single control treatment group in a seamless adaptive trial or (ii) test an experimental treatment against a single control treatment group in a seamless adaptive trial with co-primary analyses in a pre-defined subgroup and the full population.

In setting (i) test treatments are compared to the control treatment using Dunnett's many-to-one testing procedure, with an interim analysis undertaken using an early outcome measure. A decision is made on which of the treatments to take forward using a pre-defined selection rule. Data are simulated for the final outcome measure that is correlated with the early outcome measure. Data from the interim and final analyses for the final outcome measure are combined together using either the inverse normal or Fisher combination test and hypotheses are either rejected or accepted after controlling the familywise error rate at the selected level.

In setting (ii) an interim analysis is undertaken using an early outcome measure and a decision is made on whether to continue with both full and subpopulations, the subpopulation only or the full population, using a pre-defined selection rule. A number of different methods to control the family wise error rate are implemented. Data are simulated for the early and final outcome measures, subpopulation prevalence and correlation between the final and the early outcomes.

Details

Package: asd
Type: Package
Version: 2.2
Date: 2016-05-23
License: GPL-3

Simulations are run using the functions (i) `treatsel.sim` and (ii) `subpop.sim`. The other functions are not generally to be called by the user.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Some useful references to adaptive designs and more specifically to the methodology described here:

Thall PF, Simon R, Ans Ellenberg SS. A two-stage design for choosing amongst several experimental treatments and a control in clinical trials. *Biometrics* 1988;45:537-547.

Thall PF, Simon, R, Ans Ellenberg SS. Two-stage selection and testing designs for comparative clinical trials. *Biometrika* 1989;75:303-310.

Bauer P, Kieser M. Combining different phases in the development of medical treatments within a single trial. *Statistics in Medicine* 1999;18:1833-1848.

Stallard N, Todd S. Sequential designs for phase II and phase III clinical trials incorporating treatment selection. *Statistics in Medicine* 2003;22:689-703.

Posch M, Koenig F, Branson M, Brannath W, Dunger-Baldauf C, Bauer P. Testing and estimation in flexible group sequential designs with adaptive treatment selection. *Statistics in Medicine* 2005;24:3697-3714.

Bretz F, Schmidli H, Koenig F, Racine A, Maurer W. Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: General concepts. *Biometrical Journal* 2006;48:623-634.

Koenig F, Brannath W, Bretz F, Posch M. Adaptive Dunnett tests for treatment selection. *Statistics in Medicine* 2008;27:1612-1625.

Stallard N, Friede T. A group-sequential design for clinical trials with treatment selection. *Statistics in Medicine* 2008;27:6209-6227.

Friede T, Parsons N, Stallard N, Todd S, Valdes Marquez E, Chataway J, Nicholas R. Designing a Seamless Phase II/III Clinical Trial using Early Outcomes for Treatment Selection: an Application in Multiple Sclerosis. *Statistics in Medicine* 2011;30:1528-1540.

Parsons N, Friede T, Todd S, Valdes Marquez E, Chataway J, Nicholas R, Stallard N. An R package for implementing simulations for seamless phase II/III clinicals trials using early outcomes for treatment selection. *Computational Statistics and Data Analysis* 2012;56:1150-1160.

Friede T, Parsons N, Stallard N. A conditional error function approach for subgroup selection in adaptive clinical trials. *Statistics in Medicine* 2012;31:4309-4320.

See Also

[treatsel.sim](#), [subpop.sim](#)

combn.test

Combination Tests for ASD

Description

Implements weighted inverse normal and Fisher combination tests for combining p -values for adaptive seamless designs.

Usage

```
combn.test(stage1, stage2, weight = 0.5, method = "invnorm")
```

Arguments

stage1	Output from function <code>dunnett.test</code> from stage 1 of an ASD
stage2	Output from function <code>dunnett.test</code> from stage 2 of an ASD
weight	Weight indicating how p -values from stages 1 and 2 are combined; default weight is 0.5 indicating equal weighting between stages ($0 < \text{weight} < 1$)
method	Select combination test method; available options are "invnorm" or "fisher", with default "invnorm"

Details

The basic ideas of the combination test approach were proposed by Bauer and Kieser (1999) and make use of a combination function (Bauer and Kohne, 1994) to combine stagewise p -values to allow for interim adaptations and the application of the closed test principle (Marcus *et al.*, 1976) to control the overall test size across multiple hypotheses.

Value

method	Selected method of combining p -values
zscores	Z-scores for each hypothesis
hyp.comb	A list of matrices indicating the structure of the intersection hypotheses
weights	Weights used for each stage

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

- Bauer P, Kieser M. Combining different phases in the development of medical treatments within a single trial. *Statistics in Medicine* 1999;18:1833-1848.
- Bauer P, Kohne K. Evaluation of experiments with adaptive interim analyses. *Biometrics* 1994;50:1029-1041.
- Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976;63:655-660.
- Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. *Biometrics* 1999;55:1286-1290.

See Also

[treatsel.sim](#), [dunnett.test](#), [hyp.test](#), [select.rule](#), [simeans.binormal](#)

Examples

```
stage1 <- dunnett.test(c(0.75,1.5,2.25))
stage2 <- dunnett.test(c(0.15,1.75,2.15))
combn.test(stage1,stage2,weight=0.5,method="invnorm")
```

dunnett.test	<i>Dunnett Test</i>
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Description

Implements Dunnett's test (Dunnett, 1955) for many-to-one comparisons.

Usage

```
dunnett.test(Z = Z, select = rep(1, length(Z)))
```

Arguments

Z	A vector of test statistics
select	A vector of length Z; to include treatments set values to one and to exclude treatments set values to zero

Details

A many-to-one comparison test for the the null hypothesis that all the treatment effects are equal to zero against the alternative that at least one is larger than zero.

Value

pvalues	A list of matrices of p -values for all intersection hypotheses
zscores	A list of matrices of z-scores for all intersection hypotheses
hyp.comb	A list of matrices indicating the structure of the intersection hypotheses

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association* 1955;50:1096-1121.

See Also

[treatsel.sim](#), [combn.test](#), [hyp.test](#), [select.rule](#), [simeans.binormal](#)

Examples

```
dunnett.test(c(0.75,1.5,2.25))

# select two treatments only
dunnett.test(c(0.75,1.5,2.25),select=c(1,1,0))

# set test statistic to -Inf
dunnett.test(c(0.75,1.5,-Inf))
```

gsubpop.sim

ASD simulation for subpopulation selection

Description

Function `gsubpop.sim` runs simulations for a trial design that tests an experimental treatment against a single control treatment group in a seamless adaptive trial with co-primary analyses in a pre-defined subgroup and the full population. An interim analysis is undertaken using an early outcome measure and a decision is made on whether to continue with both full and subpopulations, the subpopulation only or the full population, using a pre-defined selection rule. A number of different methods to control the family wise error rate are implemented; (i) the treatment is compared to the control in the subpopulation and full populations using Simes test and the inverse normal combination function used to combine p-values before and after design adaptation, (ii) as (i) but the bivariate normal method of Spiessens and Debois (2010) is used to control the type I error rate, (iii) as (i) but a Bonferroni test is used and (iv) a conditional error function approach using the Spiessens and Debois test. Data are simulated for the early and final outcome measures, subpopulation prevalence and correlation between the final and the early outcomes. This function should not generally be called by the user. The more user-friendly function `subpop.sim` covers most common applications.

Usage

```
gsubpop.sim(z.early=NULL,z1=z1,z2=z2,sprev=sprev,
            corr=NULL,selim=NULL,nsim=nsim,seed=12345678,
            level=level,select="thresh",wt=NULL,method="CT-SD")
```

Arguments

<code>z.early</code>	Vector of test statistics for early outcome subpopulation and full population i.e. <code>c(sub, full)</code>
<code>z1</code>	Vector of test statistics for final outcome subpopulation and full population i.e. <code>c(sub, full)</code>
<code>z2</code>	Vector of test statistics for final outcome subpopulation and full population, and subpopulation and full population when both are selected i.e. <code>c(sub only, full only, sub, full)</code>
<code>sprev</code>	Subpopulation prevalence

corr	Correlation between early and final outcomes
selim	Upper and lower limits for the difference between test statistics for the threshold rule
nsim	Number of simulations (maximum=10,000,000)
seed	Seed number
level	Test level (default=0.025)
select	Selection rule type; available options are “thresh” and “futility”
wt	User set weight for combination test
method	Test type; available options are “CT-Simes”, “CT-SD”, “CT-Bonferroni” or “CEF”

Details

A structured description of the methodology and the simulation model is given by Friede *et al.* (2012).

Value

results	Table of counts; (i) the number of times the subpopulation, full population or both population are selected (n), (ii) the number of times the subpopulation is rejected when either it alone or both populations are selected (Hs), (iii) the number of times the full population is rejected when either it alone or both populations are selected (Hf), (iv) the number of times both populations are rejected (Hs+Hf) and (v) the number of times the intersection hypothesis is rejected (Hs+f)
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Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Spiessens B, Debois M. Adjusted significance levels for subgroup analysis in clinical trials. *Contemporary Clinical Trials* 2010;31:647-656.

Jenkins M, Stone A, Jennison C. An adaptive seamless phase II/III design for oncology trials with subpopulation selection using survival endpoints. *Pharmaceutical Statistics* 2011;10:347-356.

Friede T, Parsons N, Stallard N. A conditional error function approach for subgroup selection in adaptive clinical trials. *Statistics in Medicine* 2012;31:409-4320.

See Also

[subpop.sim](#)

Examples

```
gsubpop.sim(z.early=c(-1,-1),z1=c(-1,-1),z2=c(-1,0,-1,0),sprevc=c(0.5,0.5),
  corr=0.5,selim=c(-0.5,0.5),nsim=100,seed=12345678,level=0.025,
  select="thresh",wt=0.5,method="CT-SD")
```

 gtreatsel.sim

ASD simulation for treatment selection

Description

Function `treatsel.sim` runs simulations for a trial design that tests a number of experimental treatments against a single control treatment group in a seamless adaptive trial. Test treatments are compared to the control treatment using Dunnett's many-to-one testing procedure. An interim analysis is undertaken using an early outcome measure for each treatment (and control). A decision is made on which of the treatments to take forward, using a pre-defined selection rule. Data are simulated for the final outcome measure, and data from the interim and final analyses for the final outcome measure are combined together using either the inverse normal or Fisher combination test, and hypotheses tested at the selected level. This function should not generally be called by the user. The more user-friendly function `treatsel.sim` covers most common applications.

Usage

```
gtreatsel.sim(z1=c(0,0,0),z2=c(0,0,0),zearly=c(0,0,0),v1=c(1,1,1,1),
  v2=c(1,1,1,1),vearly=c(1,1,1,1),corr=0,weight=0.5,
  nsim=1000,seed=12345678,select=0,epsilon=1,thresh=1,
  level=0.025,ptest=seq(1:length(z1)),fu=FALSE,
  method="invnorm")
```

Arguments

<code>z1</code>	Vector of test statistics for the final outcome measure based on stage 1 data
<code>z2</code>	Vector of test statistics for the final outcome measure based on stage 2 data
<code>zearly</code>	Vector of test statistics for the early outcome measure
<code>v1</code>	Vector of variances for the final outcome measure based on stage 1 data; in format control treatment variance followed by the test treatment variances
<code>v2</code>	Vector of variances for the final outcome measure based on stage 2 data; format as <code>v1</code>
<code>vearly</code>	Vector of variances for the early outcome measure; format as <code>v1</code>
<code>corr</code>	Vector of correlations between the early and final outcome measures for the control and test treatments; format as <code>v1</code>
<code>weight</code>	Weighting between stages 1 and 2; default is for equal weighting (0.5)
<code>nsim</code>	Number of simulations (maximum=10,000,000)

seed	Seed number
select	Selection rule type; 0 = select all treatments, 1 = select maximum, 2 = select maximum two, 3 = select maximum three, 4 = epsilon rule (select means within epsilon of maximum), 5 = randomly select a single treatment and 6 = threshold rule (select means greater than or equal to threshold). See select.rule
epsilon	For select = 4, set epsilon criterion
thresh	For select = 6, set threshold criterion
level	Test level (default=0.025)
ptest	Vector of treatment numbers for determining power; for example, c(1,2) will count rejections of one or both hypotheses for testing treatments 1 and 2 against control
fu	Logical indicating whether patients from dropped treatments (after interim selection) should be followed-up; default TRUE
method	Select combination method; available options are “invnorm” or “fisher”, with default “invnorm”

Details

A structured description of the methodology and the simulation model is given by Friede *et al.* (2011) and implementation by Parsons *et al.* (2012).

Value

count.total	Number of times one or more treatments are selected
select.total	Number of times each test treatment is selected
reject.total	Number of times each hypothesis is rejected
sim.reject	Number of times one or more of the treatments selected using ptest is rejected

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Friede T, Parsons N, Stallard N, Todd S, Valdes Marquez E, Chataway J, Nicholas R. Designing a Seamless Phase II/III Clinical Trial using Early Outcomes for Treatment Selection: an Application in Multiple Sclerosis. *Statistics in Medicine* 2011;30:1528-1540.

Parsons N, Friede T, Todd S, Valdes Marquez E, Chataway J, Nicholas R, Stallard N. An R package for implementing simulations for seamless phase II/III clinicals trials using early outcomes for treatment selection. *Computational Statistics and Data Analysis* 2012;56:1150-1160.

See Also

[treatsel.sim](#)

Examples

```
gtreatsel.sim(z1=c(1,0,2),z2=c(1,0,2),zearly=c(1,0,1),
v1=c(1,1,1,1),v2=c(1,1,1,1),vearly=c(1,1,1,1),
corr=0,weight=0.25,nsim=100,seed=12345678,
select=1,level=0.025,ptest = c(1:3),method="fisher")
```

hyp.test

*Closed Testing for ASD***Description**

Implements the closure principle (Marcus *et al.*, 1976) for controlling the familywise type I error rate in ASD.

Usage

```
hyp.test(comb.test, level = level, full.hyp = FALSE)
```

Arguments

comb.test	Output from function combn.test
level	Test level (default=0.025)
full.hyp	Logical indicating whether the full set of intersection hypotheses should be reported; default FALSE

Details

In order to control the familywise type I error rate in the strong sense at the pre-specified level α the closure principle (Marcus *et al.*, 1976) is applied. This means that an individual null hypothesis is rejected if and only if all intersection hypotheses are also rejected at level α .

Value

reject	Matrix indicating whether elementary hypotheses have been rejected
all.rejects	Matrix indicating rejections for each intersection hypothesis, if full.hyp=TRUE
all.hyp	Matrix labelling each intersection hypothesis, if full.hyp=TRUE

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976;63:655-660.

See Also

[treatsel.sim](#), [dunnett.test](#), [combn.test](#), [select.rule](#), [simeans.binormal](#)

Examples

```
stage1 <- dunnett.test(c(0.75,1.5,2.25))
stage2 <- dunnett.test(c(0.15,1.75,2.15))
comb.test <- combn.test(stage1,stage2,weight=0.5)
hyp.test(comb.test,level=0.025,full.hyp=FALSE)

# more output
hyp.test(comb.test,level=0.025,full.hyp=TRUE)
```

select.rule

Selection Rules for Interim Analysis in ASD

Description

Function `select.rule` provides a number of options for selecting treatments at an interim analysis in ASD.

Usage

```
select.rule(x, type = 0, epsilon = 1, thresh = 1)
```

Arguments

<code>x</code>	Vector of test statistics.
<code>type</code>	Decision rule type; 0, 1, 2, 3, 4, 5 or 6 (see below for details); default is 0.
<code>epsilon</code>	For type = 4, set epsilon criterion
<code>thresh</code>	For type = 6, set threshold criterion

Details

There are seven types of selection rule available:

- (0) Select all treatments
- (1) Select one treatment; largest value of x
- (2) Select two treatments; two largest values of x
- (3) Select three treatments; three largest values of x
- (4) Epsilon rule; select all x within epsilon of maximum
- (5) Randomly select one treatment
- (6) Threshold rule; select all x larger than `thresh`

Value

select	Indicator vector that shows treatments selected (1) or not selected (0)
z	Vector of same length as select set to -Inf if not selected and 0 otherwise. For use with function <code>dunnett.test</code>

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

See Also

[treatsel.sim](#), [dunnett.test](#), [hyp.test](#), [combn.test](#), [simeans.binormal](#)

Examples

```
# select maximum treatment
select.rule(x=c(5.3,5.2,1.3,4.5,-1.3),type=4,epsilon=1)
```

simeans.binormal *Simulate Bivariate Normal Means*

Description

Simulates bivariate normal means; for use with `asd.sim` and `gasd.sim` in ASD.

Usage

```
simeans.binormal(n = n, means = means, vars = vars, corr = corr)
```

Arguments

n	Number of records used to calculate means
means	Vector of expected means for two samples
vars	Vector of expected variances for two samples
corr	Correlation between two samples

Details

Uses function `rmvnorm` from package `mvtnorm` to generate means from correlated normal variates.

Value

samp1	Mean of sample 1
samp2	Mean of sample 2

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

See Also

[treatsel.sim](#), [dunnett.test](#), [hyp.test](#), [select.rule](#), [combn.test](#)

Examples

```
# need to load mvtnorm
library(mvtnorm)

# generate data
set.seed(1234)
simeans.binormal(n=10,means=c(2,3),vars=c(1,5),corr=0.5)
```

subpop.sim

ASD simulation for subpopulation selection

Description

Function `subpop.sim` runs simulations for a trial design that tests an experimental treatment against a single control treatment group in a seamless adaptive trial with co-primary analyses in a pre-defined subgroup and the full population. An interim analysis is undertaken using an early outcome measure and a decision is made on whether to continue with both full and subpopulations, the subpopulation only or the full population, using a pre-defined selection rule. A number of different methods to control the family wise error rate are implemented; (i) the treatment is compared to the control in the subpopulation and full populations using Simes test and the inverse normal combination function used to combine p-values before and after design adaptation, (ii) as (i) but the bivariate normal method of Spiessens and Debois (2010) is used to control the type I error rate, (iii) as (i) but a Bonferroni test is used and (iv) a conditional error function approach using the Spiessens and Debois test. Data are simulated for the early and final outcome measures, subpopulation prevalence and correlation between the final and the early outcomes.

Usage

```
subpop.sim(n=list(stage1=32,enrich=NULL,stage2=32),
           effect=list(early=c(0,0),final=c(0,0)),
           outcome=list(early="N",final="N"),
           control=list(early=NULL,final=NULL),spreval=0.5,
           nsim=1000,corr=0,seed=12345678,select="thresh",
           weight=NULL,selim=NULL,level=0.025,method="CT-SD",
           spreval.fixed=TRUE,file="")
```

Arguments

n	List giving sample sizes for each treatment group at stage 1 (interim) and stage 2 (final) analyses; <code>enrich</code> allows for sample size modifications if the subgroup only is selected at stage 1
effect	List giving effect sizes for early and final outcomes
outcome	List giving outcome type for early and final outcomes; available options are “N”, “T” and “B”, for normal, time-to-event and binary data
control	Optional list giving effect sizes for early and final outcomes
sprev	Subpopulation prevalence
nsim	Number of simulations (maximum=10,000,000)
corr	Correlation between early and final outcomes
seed	Seed number
select	Selection rule type; available options are “thresh” and “futility”
weight	Optional user set weight for combination test; default is to use those suggested by Jenkins <i>et al.</i> (2011)
selim	Upper and lower limits for the difference between test statistics for the threshold rule
level	Test level (default=0.025)
method	Test type; available options are “CT-Simes”, “CT-SD”, “CT-Bonferroni” or “CEF”
sprev.fixed	Logical indicating whether subpopulation prevalence is fixed at each simulation; default TRUE
file	File name to dump output; if unset will default to R console

Details

A structured description of the the methodology and the simulation model is given by Friede *et al.* (2012).

Value

results	Table of counts; (i) the number of times the subpopulation, full population or both population are selected (n), (ii) the number of times the subpopulation is rejected when either it alone or both populations are selected (H_s), (iii) the number of times the full population is rejected when either it alone or both populations are selected (H_f), (iv) the number of times both populations are rejected (H_s+H_f) and (v) the number of times the intersection hypothesis is rejected (H_s+f)
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Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Spiessens B, Debois M. Adjusted significance levels for subgroup analysis in clinical trials. *Contemporary Clinical Trials* 2010;31:647-656.

Jenkins M, Stone A, Jennison C. An adaptive seamless phase II/III design for oncology trials with subpopulation selection using survival endpoints. *Pharmaceutical Statistics* 2011;10:347-356.

Friede T, Parsons N, Stallard N. A conditional error function approach for subgroup selection in adaptive clinical trials. *Statistics in Medicine* 2012;31:409-4320.

See Also

[gsubpop.sim](#)

Examples

```
# hazard ratio in subgroup = 0.6 and full population = 0.9
# for both early and final time-to-event outcomes
# subgroup prevalence = 0.3 and correlation = 0.5
# futility stopping rule, with limits 0 and 0
subpop.sim(n=list(stage1=100,enrich=200,stage2=300),
           effect=list(early=c(0.6,0.9),final=c(0.6,0.9)),
           spreval=0.3,outcome=list(early="T",final="T"),nsim=100,
           corr=0.5,seed=1234,select="futility",weight=NULL,
           selim=c(0,0),level=0.025,method="CT-SD",file="")
```

treatsel.sim

ASD simulation for treatment selection

Description

Function `treatsel.sim` runs simulations for a trial design that tests a number of experimental treatments against a single control treatment group in a seamless adaptive trial. Test treatments are compared to the control treatment using Dunnett's many-to-one testing procedure. An interim analysis is undertaken using an early outcome measure for each treatment (and control). A decision is made on which of the treatments to take forward, using a pre-defined selection rule. Data are simulated for the final outcome measure, and data from the interim and final analyses for the final outcome measure are combined together using either the inverse normal or Fisher combination test, and hypotheses tested at the selected level.

Usage

```
treatsel.sim(n=list(stage1=32,stage2=32),
             effect=list(early=c(0,0,0),final=c(0,0,0)),
             outcome=list(early="N",final="N"),nsim=1000,
             corr=0,seed=12345678,select=0,epsilon=1,
             weight=NULL,thresh=1,level=0.025,ptest=c(1),
             method="invnorm",fu=FALSE,file = "")
```

Arguments

n	List giving sample sizes for each treatment group at stage 1 (interim) and stage 2 (final) analyses
effect	List giving effect sizes for early and final outcomes
outcome	List giving outcome type for early and final outcomes; available options are “N”, “T” and “B”, for normal, time-to-event and binary data
nsim	Number of simulations (maximum=10,000,000)
corr	Correlation between early and final outcomes
seed	Seed number
select	Selection rule type (select.rule); 0 = select all treatments, 1 = select maximum, 2 = select maximum two, 3 = select maximum three, 4 = epsilon rule (select means within epsilon of maximum), 5 = randomly select a single treatment and 6 = threshold rule (select means greater than or equal to threshold)
epsilon	For select = 4, set epsilon criterion
weight	Optional user set weight for combination test; default is to use those suggested by Jenkins <i>et al.</i> (2011)
thresh	For select = 6, set threshold criterion
level	Test level (default=0.025)
ptest	Vector of treatment numbers for determining power; for example, c(1,2) will count rejections of one or both hypotheses for testing treatments 1 and 2 against the control
method	Select combination method; available options are “invnorm” or “fisher”, with default “invnorm”.
fu	Logical indicating whether patients from dropped treatments (after interim selection) should be followed-up; default FALSE
file	File name to dump output; if unset will default to R console

Details

A structured description of the the methodology and the simulation model is given by Friede *et al.* (2011) and implementation by Parsons *et al.* (2012).


```
outcome=list(early="N",final="N"),  
nsim=200,corr=0.3,seed=145514,select=4,epsilon=1,  
level=0.025,ptest=c(1:5),method="invnorm")
```

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