Package 'AGSDest'

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Type Package

Title Estimation in Adaptive Group Sequential Trials

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Imports stats, graphics, grDevices, ldbounds

Description Calculation of repeated confidence intervals as well as confidence intervals based on the stage-wise ordering in group sequential designs and adaptive group sequential designs. For adaptive group sequential designs the confidence intervals are based on the conditional rejection probability principle. Currently the procedures do not support the use of futility boundaries or more than one adaptive interim analysis.

License GPL (>= 2)

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adapt *Adaptations in group sequential trials*

Description

adapt is a function that performs adaptations and plans the secondary group sequential trial. The effect size used for planning the secondary trial is a weighted mean between the interim estimate theta and the initially assumed estimate delta (pT\$delta) of the primary trial.

Usage

```
adapt(pT, iD, SF, phi, cp, theta = iD$z/(pT$t[iD$T] * pT$Imax), I2min, I2max,
  swImax, delta = pT$delta, weight = 1, warn = TRUE)
```

Arguments

pT	object of the class GSTobj; primary trial design
iD	interim data; a list with the variables T and z; list(T = stage of interim analysis, z = interim z-statistic)
SF	spending function for the secondary trial
phi	parameter of spending function for the secondary trial when SF=3 or 4 (See below)
cp	conditional power
theta	new effect size (default: estimate from interim analysis)
I2min	minimal total information of secondary trial
I2max	maximal total information of secondary trial
swImax	maximal incremental information per stage
delta	initially assumed effect size for the primary trial (default: estimate from primary trial)
weight	weight of theta when updating the effect size estimate as weighted mean of theta and delta
warn	option if warnings should be printed to the screen (default: true)

Details

If no adaptation is performed then this indicates that the original plan is kept. In this case sT is set to NULL. If an adaptation is performed sT is a list which contains the following elements:

K	number of stages
a	lower critical bounds of secondary group sequential design(are currently always set to -8)
b	upper critical bounds of secondary group sequential design
t	vector with cumulative information fractions
al	alpha (type I error rate); equal to the conditional type I error rate of the primary trial

SF	spending function
phi	parameter of spending function when SF=3 or 4 (See below)
alab	alpha-absorbing parameter values of secondary group sequential design
als	alpha-values "spent" at each stage of secondary group sequential design
Imax	maximum information number
delta	effect size used for planning the secondary trial
cp	conditional power

A value of SF=3 is the power family. Here, the spending function is t^{ϕ}, where phi must be greater than 0. A value of SF=4 is the Hwang-Shih-DeCani family, with the spending function $(1 - e^{-\phi t})/(1 - e^{-\phi})$, where phi cannot be 0.

Value

adapt returns an object of the class GSTobj; the design of the secondary trial. The adaptation rule is as in the first simulation example of Brannath et al.(2008). If no adaptations are performed, the function returns sT = NULL. An object of class GSTobj is a list containing the following components:

sT	secondary trial

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

References

Brannath, W, Mehta, CR, Posch, M (2008) "Exact confidence bounds following adaptive group sequential tests", *Biometrics* accepted.

See Also

GSTobj, print.GSTobj, plot.GSTobj, plan.GST

Examples

```
##The following performs an adaptation of the sample size and
##number of interim analyses after the first stage of the primary trial.

pT=plan.GST(K=3,SF=4,phi=-4,alpha=0.05,delta=6,pow=0.9,compute.alab=TRUE,compute.als=TRUE)

iD=list(T=1, z=1.090728)

swImax=0.0625

I2min=3*swImax
I2max=3*swImax

sT=adapt(pT=pT,iD=iD,SF=1,phi=0,cp=0.8,theta=5,I2min,I2max,swImax)
```

AGSDest *Estimation in adaptive group sequential trials*

Description

The package allows to compute repeated confidence intervals as well as confidence intervals based on the stage-wise ordering in groug sequential designs (GSD; see Jennison and Turnbull, 1989; Tsiatis, Rosner, Mehta, 1984) and adaptive groug sequential designs (Mehta, Bauer, Posch, Brannath, 2007; Brannath, Mehta, Posch, 2008). For adaptive group sequential designs the confidence intervals are based on the conditional rejection probability principle of Mueller and Schaefer (2001). This principle allows us to perform data dependent changes to the sample size, the spending function, and the number and spacing of interim looks while preserving the overall type I error rate. Currently the procedures do not support the use of futility boundaries as well as more than one adaptive interim analysis. Furthermore, the package is currently restricted to the computation of lower one-sided confidence intervals.

Details

Package: AGSDest

Type: Package Version: 2.2 Date: 2015-01-12 License: GPL Version 2 or later

Main functions: `adapt`: Performs adaptations at an interim analysis of a GSD to the sample size, number of interim stages and spending function based on the conditional power in a GSD at an interim analysis; the result is a secondary trial `plan.GST`: Plans a group sequential trial `cer`: Computes the conditional type I error rate (also called conditional rejection probability) of a GSD at an interim analysis `typeIerr`: Computes the type I error rate of a GSD `pvalue`: Computes the repeated or stage-wise adjusted p-value for a classical GSD or for a GSD with design adaptations `seqconfint`: Computes the repeated confidence bound and confidence bound based on the stage-wise ordering for a GSD or for a GSD with design adaptations

Subfunctions: `as.GST`: Builds a group sequential trial object `as.AGST`: Builds an adaptive group sequential trial object

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

References

Brannath, W, Mehta, CR, Posch, M (2008) "Exact confidence bounds following adaptive group sequential tests", *Biometrics* accepted.

Jennison, C, Turnbull, BW (1989) "Repeated confidence intervals for group sequential clinical trials", *Contr. Clin. Trials*, 5, 33-45.

Mehta, CR, Bauer, P, Posch, M, Brannath, W (2007) "Repeated confidence intervals for adaptive group sequential trials", *Statistics in Medicine*, 26, 5422-5433.

Mueller, HH, Schaefer, H (2001) "Adaptive group sequential design for clinical trials: Combining the advantages of adaptive and of classical group sequential approaches", *Biometrics*, 57, 886-891.

O'Brien, PC, Fleming, TR (1979) "A multiple testing procedure for clinical trials", *Biometrics*, 35 , 549-556

Schoenfeld, D (2001) "A simple Algorithm for Designing Group Sequential Clinical Trials", *Biometrics*, 27, 972-974

Tsiatis,AA, Rosner,GL, Mehta,CR (1984) "Exact confidence intervals following a group sequential test", *Biometrics*, 40, 797-804.

Examples

```
pT=plan.GST(K=3,SF=4,phi=-4,alpha=0.05,delta=6,pow=0.9,compute.alab=TRUE,compute.als=TRUE)

iD=list(T=1, z=1.090728)

swImax=0.0625

I2min=3*swImax
I2max=3*swImax

sT=adapt(pT=pT,iD=iD,SF=1,phi=0,cp=0.8,theta=5,I2min,I2max,swImax)
sTo=list(T=2, z=2.393)
AGST <- as.AGST(pT=pT,iD=iD,sT=sT,sTo=sTo)

##The following calculates the stage-wise adjusted p-value
##of a group sequential trial after a design adaptation
pvalue(AGST,type="so")

##and the corresponding confidence bound based on the stage-wise ordering.
seqconfint(AGST,type="so")

##Both, the p-value and the confidence interval can be calculated by
##the summary function
## Not run:
summary(AGST,ctype="so",ptype="so")

## End(Not run)
```

`AGSTobj` *Adaptive group sequential trial object (AGSTobj)*

Description

The `AGSTobj` includes design and outcome of primary and secondary trial.

Usage

```
AGSTobj(x, ...)

## S3 method for class 'AGSTobj'
plot(x, main = c("primary trial", "secondary trial"),
```

```
  print.pdf = FALSE, ...)

## S3 method for class 'AGSTobj'
print(x, ...)

## S3 method for class 'AGSTobj'
summary(object, ctype = c("r", "so"), ptype = c("r",
  "so"), etype = c("ml", "mu", "cons"), overwrite = FALSE, ...)

## S3 method for class 'summary.AGSTobj'
print(x, ...)
```

Arguments

x	object of the class AGSTobj
...	additional arguments.
main	Title of the plots (default: first plot: "primary trial"; second plot: "secondary trial")
print.pdf	option; if TRUE a pdf file is created. Instead of setting print.pdf to TRUE, the user can specify a character string giving the name or the path of the file.
object	object of the class AGSTobj
ctype	confidence type: repeated "r" or stage-wise ordering "so" (default: c("r", "so"))
ptype	p-value type: repeated "r" or stage-wise ordering "so" (default: c("r", "so"))
etype	point estimate: maximum likelihood "ml", median unbiased "mu", or conservative "cons" (default: c("ml", "mu", "cons"))
overwrite	option; if TRUE all old values are deleted and new values are calculated (default: FALSE)

Details

A AGSTobj object is designed.

The function summary returns an object of class AGSTobj. ctype defines the type of confidence interval that is calculated.

"r"	Repeated confidence bound for a GSD with design adaptations
"so"	Confidence bound for a GSD with design adaptation based on the stage-wise ordering

The calculated confidence bounds are saved as:

cb.r	repeated confidence bound
cb.so	confidence bound based on the stage-wise ordering

ptype defines the type of p-value that is calculated.

"r"	Repeated p-value for a GSD with design adaptations
"so"	Stage-wise adjusted p-value for a GSD with design adaptations

'

The calculated p-values are saved as:

pvalue.r	repeated p-value
pvalue.so	stage-wise adjusted p-value

etype defines the type of point estimate

"ml"	maximum likelihood estimate (ignoring the sequential and adaptive nature of the design)
"mu"	median unbiased estimate (stage-wise lower confidence bound at level 0.5) for a GSD with design adaptations
"cons"	conservative estimate (repeated lower confidence bound at level 0.5) for a GSD with design adaptations

The calculated point estimates are saved as:

est.ml	Maximum likelihood estimate
est.mu	Median unbiased estimate
est.cons	Conservative estimate

The stage-wise adjusted confidence bound, p-value and the median unbiased point estimate can only be calculated at the stage where the trial stops and are only valid if the stopping rule is met.

The repeated confidence bound, repeated p-value, conservative estimate and maximum likelihood estimate can be calculated at every stage of the trial and not just at the stage where the trial stops and are also valid if the stopping rule is not met. For calculating the repeated confidence bounds or p-values the user has to specify sTo (secondary trial outcome) in the object AGSTobj (see example below). If the stopping rule is not met in object sTo then sta e-wise adjusted confidence bounds and p-values will not be computed while a warning message is given when their computation have erroneously been specified.

Value

An object of class AGSTobj, which is basically a list with the elements

cb.so	confidence bound based on the stage-wise ordering (stage-wise adjusted confidence bound)
cb.r	repeated confidence bound
pvalue.so	p-value based on the stage-wise ordering (stage-wise adjusted p-value)
pvalue.r	repeated p-value
est.ml	maximum likelihood estimate
est.mu	median unbiased point estimate
est.cons	conservative point estimate

pT	
K	number of stages
al	alpha (type I error rate)
a	lower critical bounds of primary group sequential design (are currently always set to -8)
b	upper critical bounds of primary group sequential design
t	vector with cumulative information fraction
SF	spending function (for details see below)
phi	parameter of spending function when SF=3 or 4 (for details see below)
alab	alpha-absorbing parameter values of primary group sequential design
als	alpha-values "spent" at each stage of primary group sequential design
Imax	maximum information number
delta	effect size used for planning the primary trial
cp	conditional power for planning the primary trial
iD	
L	stage of the adaptation
z	z-statistic at adaptive interim analysis
sT	
K	number of stages
al	conditional rejection probability
a	lower critical bounds of secondary group sequential design (are currently always set to -8)
b	upper critical bounds of secondary group sequential design
t	vector with cumulative information fraction
SF	spending function (for details see below)
phi	parameter of spending function when SF=3 or 4 (for details see below)
Imax	maximum information number
delta	effect size used for planning the secondary trial
cp	conditional power for planning the secondary trial
sTo	
T	stage where trial stops
z	z-statistic at stage where trial stops

Note

The AGSTobj should always have the same ordering and names as given in the list above or as given in the example. 1. pt, 2. iD, 3. sT, 4. sTo SF defines the spending function. SF = 1 O'Brien and Fleming type spending function of Lan and DeMets (1983) SF = 2 Pocock type spending function of Lan and DeMets (1983) SF = 3 Power family ($c_\alpha * t^\phi$); phi must be greater than 0. SF = 4 Hwang-Shih-DeCani family;$(1 - e^{-\phi t})/(1 - e^{-\phi})$, where phi cannot be 0. A value of SF=3 corresponds

to the power family. Here, the spending function is t^{ϕ}, where phi must be greater than 0. A value of SF=4 corresponds to the Hwang-Shih-DeCani family, with the spending function $(1 - e^{-\phi t})/(1 - e^{-\phi})$, where phi cannot be 0. If a path is specified for print.pdf, all \ must be changed to /. If a filename is specified the ending of the file must be (.pdf). In the current version the vector of lower bounds a should be set to rep(-8,K)

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

See Also

AGSTobj, print.AGSTobj, plot.AGSTobj, summary.AGSTobj

Examples

```
## Not run:
pT=plan.GST(K=3,SF=4,phi=-4,alpha=0.05,delta=6,pow=0.9,compute.alab=TRUE,compute.als=TRUE)

iD=list(T=1, z=1.090728)

swImax=0.0625

I2min=3*swImax
I2max=3*swImax

sT=adapt(pT=pT,iD=iD,SF=1,phi=0,cp=0.8,theta=5,I2min,I2max,swImax)

sTo=list(T=2, z=2.393)

AGST<-as.AGST(pT=pT,iD=iD,sT=sT,sTo=sTo)
AGST
plot(AGST)

AGST<-summary(AGST)
plot(AGST)

##The repeated confidence interval and p-value at an earlier stage
##than the one where the trial stops (T=3).

summary(as.AGST(pT,iD,sT,sTo=list(T=1,z=1.7)),ctype="r",ptype="r")

##If the stage-wise adjusted confidence interval is calculated at this stage,
##the function returns an error message
summary(as.AGST(pT,iD,sT,sTo=list(T=1,z=1.7)),ctype="so",ptype="so")

## End(Not run)
```

as.AGST *as Adaptive Group Sequential Trial*

Description

Function as.AGST builds an adaptive group sequential trial object

Usage

```
as.AGST(pT, iD, sT, sTo = NULL)
```

Arguments

pT	object of the class GSTobj; primary trial design
iD	interim data; a list with the variables T and z; list(T = stage of interim analysis, z = interim z-statistic)
sT	object of the class GSTobj; secondary trial design
sTo	secondary trial outcome; a list with the variables T and z; list(T = stage where trial stops, z = z-statistic at stage where trial stops)

Value

Returns a list containing the pT, iD, sT and sTo with class=AGSTobj

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

See Also

AGSTobj

Examples

```
pT=plan.GST(K=3,SF=4,phi=-4,alpha=0.05,delta=6,pow=0.9,compute.alab=TRUE,compute.als=TRUE)
iD=list(T=1, z=1.090728)
swImax=0.0625
I2min=3*swImax
I2max=3*swImax

sT=adapt(pT=pT,iD=iD,SF=1,phi=0,cp=0.8,theta=5,I2min,I2max,swImax)
sTo=list(T=2, z=2.393)
AGST <- as.AGST(pT=pT,iD=iD,sT=sT,sTo=sTo)
```

as.GST *as Group Sequential Trial*

Description

Function as.GST builds a group sequential trial object

Usage

```
as.GST(GSD, GSDo)
```

Arguments

GSD	object of the class GSTobj; group sequential design
GSDo	group sequential design outcome; a list with the variables T and z; list(T = stage where trial stops, z = z-statistic at stage where trial stops)

Value

Returns a list containing the GSD and GSDo with class=GSTobj

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

See Also

GSTobj

Examples

```
GSD <- plan.GST(K=4,SF=1,phi=0,alpha=0.025,delta=6,pow=0.8,compute.alab=TRUE,compute.als=TRUE)
GSDo <- list(T=2, z=3.1)
GST <- as.GST(GSD=GSD,GSDo=GSDo)
GST
```

cer *Conditional type I error rate (also called conditional rejection probability)*

Description

Calculates the conditional type I error rate of a GSD

Usage

```
cer(pT, iD)
```

Arguments

pT	object of the class GSTobj; primary trial design
iD	interim data; a list with the variables T and z; list(T = stage of interim analysis, z = interim z-statistic)

Value

cer conditional type I error rate

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

References

Mueller, HH, Schaefer, H (2001) "Adaptive group sequential design for clinical trials: Combining the advantages of adaptive and of classical group sequential approaches", *Biometrics*, 57, 886-891.

See Also

plan.GST

Examples

```
##The following calculates the conditional type I error rate
##under the null hypotesis after an adaptation at the second stage
##of the primary trial.
pT=plan.GST(K=4,SF=1,phi=0,alpha=0.025,delta=6,pow=0.8,compute.alab=TRUE,compute.als=TRUE)
cer(pT=pT,iD=list(T=2, z=1.09))
```

---

cp *coditional power of a GSD*

Description

cp is a function that computes the conditional power of a GSD.

Usage

```
cp(GSD)
```

Arguments

GSD	object of the class GSTobj or list with the following elements: K = number of stages, a = vector with futility boundaries (not supported yet), b = rejection boundaries, t = vector with information fractions, Imax = maximum information number, delta = effect size used for planning the trial; see example blow.

Value

cp returns the conditional power of a GSD.

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

References

O'Brien, PC, Fleming, TR (1979) "A multiple testing procedure for clinical trials", *Biometrics*, 35 , 549-556
Schoenfeld, D (2001) "A simple Algorithm for Designing Group Sequential Clinical Trials", *Biometrics*, 27, 972-974

See Also

GSTobj

Examples

```
##The following calculates the conditional power of a GSD.
GSD <- list(K=4,a=rep(-8,4),b=c(4.333,2.963,2.359,2.014),t=c(0.25,0.5,0.75,1),Imax=0.22,delta=4)
cp(GSD)
```

GSTobj *Group sequential trial object (GSTobj)*

Description

The GSTobj includes design and outcome of primary trial.

Usage

```
GSTobj(x, ...)

## S3 method for class 'GSTobj'
plot(x, main = "GSD", print.pdf = FALSE, ...)

## S3 method for class 'GSTobj'
print(x, ...)

## S3 method for class 'GSTobj'
summary(object, ctype = c("r", "so"), ptype = c("r", "so"),
  etype = c("ml", "mu", "cons"), overwrite = FALSE, ...)

## S3 method for class 'summary.GSTobj'
print(x, ...)
```

Arguments

x	object of the class GSTobj
...	additional arguments.
main	Title of the plots (default: "GSD")
print.pdf	option; if TRUE a pdf file is created. Instead of setting print.pdf to TRUE, the user can specify a character string giving the name or the path of the file.
object	object of the class GSTobj
ctype	confidence type: repeated "r" or stage-wise ordering "so" (default: c("r", "so"))
ptype	p-value type: repeated "r" or stage-wise ordering "so" (default: c("r", "so"))
etype	point estimate: maximum likelihood "ml", median unbiased "mu" or conservative "cons" (default: c("ml", "mu", "cons"))
overwrite	option; if TRUE all old values are deleted and new values are calculated (default: FALSE)

Details

A GSTobj object is designed.

The function summary returns an object of class GSTobj.

ctype defines the type of confidence interval that is calculated.

"r"	Repeated confidence bound for a classical GSD
"so"	Confidence bound for a classical GSD based on the stage-wise ordering

The calculated confidence bounds are saved as:

cb.r	repeated confidence bound
cb.so	confidence bound based on the stage-wise ordering

ptype defines the type of p-value that is calculated.

"r"	Repeated p-value for a classical GSD
"so"	Stage-wise adjusted p-value for a classical GSD

The calculated p-values are saved as:

pvalue.r	repeated p-value
pvalue.so	stage-wise adjusted p-value

etype defines the type of point estimate

"ml"	maximum likelihood estimate (ignoring the sequential nature of the design)
"mu"	median unbiased estimate (stage-wise lower confidence bound at level 0.5) for a classical GSD
"cons"	Conservative estimate (repeated lower confidence bound at level 0.5) for a classical GSD

The calculated point estimates are saved as:

est.ml	Maximum likelihood estimate
est.mu	Median unbiased estimate
est.cons	Conservative estimate

The stage-wise adjusted confidence interval and p-value and the median unbiased point estimate can only be calculated at the stage where the trial stops and is only valid if the stopping rule is met.

The repeated confidence interval and repeated p-value, conservative estimate and maximum likelihood estimate can be calculated at every stage of the trial and not just at the stage where the trial stops and is also valid if the stopping rule is not met. For calculating the repeated confidence interval or p-value at any stage of the trial the user has to specify the outcome GSDo in the object GSTobj (see example below).

Value

An object of class GSTobj, is basically a list with the elements

cb.so	confidence bound based on the stage-wise ordering
cb.r	repeated confidence bound
pvalue.so	stage-wise adjusted p-value
pvalue.r	repeated p-value
est.ml	maximum likelihood estimate
est.mu	median unbiased point estimate
est.cons	conservative point estimate
GSD	
K	number of stages
al	alpha (type I error rate)
a	lower critical bounds of group sequential design (are currently always set to -8)
b	upper critical bounds of group sequential design
t	vector with cumulative information fraction
SF	spending function (for details see below)
phi	parameter of spending function when SF=3 or 4 (for details see below)
alab	alpha-absorbing parameter values of group sequential design
als	alpha-values ”spent” at each stage of group sequential design
Imax	maximum information number

delta	effect size used for planning the primary trial
cp	conditionla power of the trial
GSDo	
T	stage where trial stops
z	z-statistic at stage where trial stops

Note

SF defines the spending function. SF = 1 O'Brien and Fleming type spending function of Lan and DeMets (1983) SF = 2 Pocock type spending function of Lan and DeMets (1983) SF = 3 Power family ($c_\alpha * t^\phi$). phi must be greater than 0. SF = 4 Hwang-Shih-DeCani family.$(1-e^{-\phi t})/(1-e^{-\phi})$, where phi cannot be 0. A value of SF=3 corresponds to the power family. Here, the spending function is t^ϕ, where phi must be greater than 0. A value of SF=4 corresponds to the Hwang-Shih-DeCani family, with the spending function $(1 - e^{-\phi t})/(1 - e^{-\phi})$, where phi cannot be 0. If a path is specified for print.pdf, all \ must be changed to /. If a filename is specified the ending of the file must be (.pdf). In the current version a should be set to rep(-8,K)

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

See Also

GSTobj, print.GSTobj, plot.GSTobj, summary.GSTobj

Examples

```
GSD=plan.GST(K=4,SF=1,phi=0,alpha=0.025,delta=6,pow=0.8,compute.alab=TRUE,compute.als=TRUE)
GST<-as.GST(GSD=GSD,GSDo=list(T=2, z=3.1))
GST
plot(GST)
GST<-summary(GST)
plot(GST)
##The repeated confidence interval, p-value and maximum likelihood estimate
##at the earlier stage T=1 where the trial stopping rule is not met.
summary(as.GST(GSD,GSDo=list(T=1,z=0.7)),ctype="r",ptype="r",etype="ml")
## Not run:
##If e.g. the stage-wise adjusted confidence interval is calculated at this stage,
##the function returns an error message
summary(as.GST(GSD,GSDo=list(T=1,z=0.7)),ctype="so",etype="mu")

## End(Not run)
```

plan.GST *Plans a group sequential trial (GST)*

Description

Plans a group sequential trial (GST)

Usage

```
plan.GST(K, t = (1:K)/K, Imax = NULL, SF, phi, alpha, delta = NULL,
  pow = NULL, compute.alab = TRUE, compute.als = TRUE)
```

Arguments

K	number of stages
t	vector with the cumulative information fraction (default: (1:K)/K)
Imax	maximum information number (default: NULL)
SF	spending function (for details see below)
phi	parameter of spending function when SF=3 or 4 (See below)
alpha	alpha (type I error rate)
delta	effect size (alternative)(default: NULL)
pow	power (default: NULL)
compute.alab	specify if alpha-absorbing parameter values should be calculated (default: TRUE)
compute.als	specify if alpha-values "spent" at every stage should be calculated (default: TRUE)

Details

The user has to specify either Imax or delta and pow. If all three items are specified, the pre-defined maximum information number is newly calculated from the information for delta and power, and Imax is overwritten.

SF defines the spending function.

SF = 1 O'Brien and Fleming type spending function of Lan and DeMets (1983)
SF = 2 Pocock type spending function of Lan and DeMets (1983)
SF = 3 Power family ($c_\alpha * t^\phi$); phi must be greater than 0
SF = 4 Hwang-Shih-DeCani family; $(1 - e^{-\phi t})/(1 - e^{-\phi})$, where phi cannot be 0

Value

plan.GST returns an object of the class GSTobj. An object of class GSTobj is a list containing the following components:

K	number of stages

a	lower critical bounds of group sequential design (are currently always set to -8)
b	upper critical bounds of group sequential design
t	vector with cumulative information fraction
al	alpha (type I error)
SF	spending function
phi	parameter of spending function when SF=3 or 4 (See below)
Imax	maximum information number
delta	effect size used for planning the primary trial

Author(s)

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References

Brannath, W, Mehta, CR, Posch, M (2008) "Exact confidence bounds following adaptive group sequential tests", *Biometrics* accepted.

See Also

GSTobj, print.GSTobj, plot.GSTobj

Examples

```
##The following plans an O'Brien and Flaming group sequential design (GSD)
##with 4 stages and equally spaced looks.
pT <- plan.GST(K=4, SF=1, phi=0, alpha=0.025, delta=6, pow=0.8, compute.alab=TRUE, compute.als=TRUE)
```

---

pvalue *Calculates the p-value*

Description

Calculates the repeated or stage-wise adjusted p-value of a GSD or a AGSD

Usage

```
pvalue(object, type = c("r", "so"))
```

Arguments

object	object of the class GSTobj or of the class AGSTobj
type	p-value type: repeated "r", stage-wise ordering "so" or both "b" (default: "b")

Details

`object` can be an object of the `class` `GSTobj` or an object of the `class` `AGSTobj`. The function identifies the `class` of the object and calculates the corresponding p-value (classical or adaptive).

If `object` has `class` `GSTobj`, then a p-value for a classical GSD is calculated. `type` defines the type of confidence interval that is calculated

`"r"`	Repeated p-value for a classical GSD
`"so"`	Stage-wise adjusted p-value for a classical GSD

If `object` has `class` `AGSTobj`, then a p-value for a GSD with design adaptation is calculated. `type` defines the type of confidence interval that is calculated

`"r"`	Repeated p-value for a GSD with design adaptations
`"so"`	Stage-wise adjusted p-value for a GSD with design adaptations

Value

The function `pvalue` returns according to the `object` the classical or adaptive p-value for the final stage. If the parameter value has the `class` `GSTobj` the classical p-value is calculated. If the parameter value has the `class` `AGSTobj` the adaptive p-value is calculated.

The calculated p-values are saved as:

`pvalue.r`	repeated p-value
`pvalue.so`	stage-wise adjusted p-value

Note

The stage-wise adjusted p-value can only be calculated at the stage where the trial stops and is only valid if the stopping rule is met.

The repeated p-value can be calculated at every stage of the trial and not just at the stage where the trial stops and is also valid if the stopping rule is not met.

For calculating the sequential p-values at stage `T` the user has to specify the outcome `GSDo` in the object `GSTobj` or `sTo` (secondary trial outcome) in the object `AGSTobj`. A trial outcome is a list of the form `list=(T=stage of interim analysis,z = interim z-statistic)`; see the example below.

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

References

Brannath, W, Mehta, CR, Posch, M (2008) "Exact confidence bounds following adaptive group sequential tests", *Biometrics* accepted.

Jennison, C, Turnbull, BW (1989) "Repeated confidence intervals for group sequential clinical trials", *Contr. Clin. Trials*, 5, 33-45.

Mehta, CR, Bauer, P, Posch, M, Brannath, W (2007) "Repeated confidence intervals for adaptive group sequential trials", *Statistics in Medicine*, 26, 5422-5433.

Mueller, HH, Schaefer, H (2001) "Adaptive group sequential design for clinical trials: Combining the advantages of adaptive and of classical group sequential approaches", *Biometrics*, 57, 886-891.

Tsiatis,AA, Rosner,GL, Mehta,CR (1984) "Exact confidence intervals following a group sequential test", *Biometrics*, 40, 797-804.

See Also

AGSTobj, GSTobj

Examples

```
##The following calculates the repeated p-value of a group sequential trial

## Not run:
GSD=plan.GST(K=4,SF=1,phi=0,alpha=0.025,delta=6,pow=0.8,compute.alab=TRUE,compute.als=TRUE)

GST<-as.GST(GSD=GSD,GSDo=list(T=2, z=3.1))

pvalue(GST,type="r")

##The stage-wise adjusted p-value of a group sequential trial is calculated by
pvalue(GST,type="so")

##The repeated p-value at the earlier stage T=1 where the trial stopping rule is not met.
pvalue(as.GST(GSD,GSDo=list(T=1,z=0.7)),type="r")

##If the stage-wise adjusted p-value is calculated at this stage,
##the function returns an error message

pvalue(as.GST(GSD,GSDo=list(T=1,z=0.7)),type="so")

##The repeated and the stage-wise adjusted p-value of a
##group sequential trial after a design adaptation is calculated by

pT=plan.GST(K=3,SF=4,phi=-4,alpha=0.05,delta=6,pow=0.9,compute.alab=TRUE,compute.als=TRUE)

iD=list(T=1, z=1.090728)

swImax=0.0625

I2min=3*swImax
I2max=3*swImax

sT=adapt(pT=pT,iD=iD,SF=1,phi=0,cp=0.8,theta=5,I2min,I2max,swImax)

sTo=list(T=2, z=2.393)
```

```
AGST<-as.AGST(pT=pT,iD=iD,sT=sT,sTo=sTo)
pvalue(AGST)

##The repeated p-value at the earlier stage T=2 where the stopping rule is not met.

pvalue(as.AGST(pT,iD,sT,sTo=list(T=2,z=1.7)),type="r")

##If the stage-wise adjusted p-value is calculated at this stage,
##the function returns an error message

pvalue(as.AGST(pT,iD,sT,sTo=list(T=2,z=1.7)),type="so")

## End(Not run)
```

`seqconfint` *Calculates confidence interval*

Description

Calculates the repeated confidence bound or the confidence bound based on the stage-wise ordering of a GSD or a AGSD

Usage

```
seqconfint(object, type = c("r", "so"), level = NULL)
```

Arguments

`object`	object of the `class` `GSTobj` or of the `class` `AGSTobj`
`type`	confidence type: repeated "r", stage-wise ordering "so" or both "b" (default: "b")
`level`	type I error rate (default: NULL)

Details

`object` can be an object of the `class` `GSTobj` or an object of the `class` `AGSTobj`. The function identifies the `class` of the object and calculates the corresponding confidence interval (classical or adaptive).

If `object` has `class` `GSTobj`, then a confidence bound for a classical GSD is calculated. `type` defines the type of confidence interval that is calculated

`"r"`	Repeated confidence bound for a classical GSD
`"so"`	Confidence bound for a classical GSD based on the stage-wise ordering

If `object` has `class` `AGSTobj`, then a confidence bound for a GSD with design adaptation is calculated. `type` defines the type of confidence interval that is calculated

`"r"`	Repeated confidence bound for a GSD with design adaptations

"so"	Confidence bound for a GSD with design adaptation based on the stage-wise ordering

By setting level to the value 0.5 the conservative point estimate is calculated. Default is the level of the primary trial.

Value

The function seqconfint returns according to the class of object the classical or adaptive confidence bound. If object has class GSTobj the classical confidence bound is calculated. If the parameter value has the class AGSTobj the adaptive confidence bound is calculated.

The calculated confidence bounds are saved as:

cb.r	repeated confidence bound
cb.so	confidence bound based on the stage-wise ordering

If the level is set to 0.5, the calculated point estimates are:

est.mu	Median unbiased point estimate, based on the stage-wise ordering
est.cons	Flexible, but conservative repeated point estimate

Note

The stage-wise adjusted confidence interval can only be calculated at the stage where the trial stops and is only valid if the stopping rule is met.

The repeated confidence interval can be calculated at every stage of the trial and not just at the stage where the trial stops and is also valid if the stopping rule is not met.

For calculating the sequential confidence intervals at stage T the user has to specify the outcome GSDo in the object GSTobj or sTo (secondary trial outcome) in the object AGSTobj. A trial outcome is a list of the form list=(T=stage of interim analysis,z = interim z-statistic); see the example below.

Author(s)

Niklas Hack <niklas.hack@meduniwien.ac.at> and Werner Brannath <werner.brannath@meduniwien.ac.at>

References

Brannath, W, Mehta, CR, Posch, M (2008) "Exact confidence bounds following adaptive group sequential tests", *Biometrics* accepted.

Jennison, C, Turnbull, BW (1989) "Repeated confidence intervals for group sequential clinical trials", *Contr. Clin. Trials*, 5, 33-45.

Mehta, CR, Bauer, P, Posch, M, Brannath, W (2007) "Repeated confidence intervals for adaptive group sequential trials", *Statistics in Medicine*, 26, 5422-5433.

Mueller, HH, Schaefer, H (2001) "Adaptive group sequential design for clinical trials: Combining the advantages of adaptive and of classical group sequential approaches", *Biometrics*, 57, 886-891.

Tsiatis,AA, Rosner,GL, Mehta,CR (1984) "Exact confidence intervals following a group sequential test", *Biometrics*, 40, 797-804.

See Also

AGSTobj, GSTobj

Examples

```
##The following calculates the repeated confidence bound of a group sequential trial

GSD <- plan.GST(K=4, SF=1, phi=0, alpha=0.025, delta=6, pow=0.8,
                compute.alab=TRUE, compute.als=TRUE)

GST <- as.GST(GSD=GSD, GSDo=list(T=2, z=3.1))
seqconfint(GST, type="r")

##The confidence bound based on the stage-wise ordering of a group sequential trial is calculated by

seqconfint(GST, type="so")

##The repeated confidence interval at the earlier stage T=1 where the
##trial stopping rule is not met.

seqconfint(as.GST(GSD, GSDo=list(T=1, z=0.7)), type="r")

##The repeated confidence bound and the confidence bound
##based on the stage-wise ordering of a group sequential trial
##after a design adaptation is calculated by

pT <- plan.GST(K=3, SF=4, phi=-4, alpha=0.05, delta=6, pow=0.9,
               compute.alab=TRUE, compute.als=TRUE)

iD <- list(T=1, z=1.090728)

swImax <- 0.0625

I2min <- 3*swImax
I2max <- 3*swImax

sT <- adapt(pT=pT, iD=iD, SF=1, phi=0, cp=0.8, theta=5, I2min, I2max, swImax)

sTo <- list(T=2, z=2.393)

AGST <- as.AGST(pT=pT, iD=iD, sT=sT, sTo=sTo)
seqconfint(AGST)

##The repeated confidence interval at the earlier stage T=2 where the
##trial stopping rule is not met.

seqconfint(as.AGST(pT, iD, sT, sTo=list(T=2, z=1.7)), type="r")

## Not run:
  ##If the stage-wise adjusted confidence interval is calculated at this stage,
  ##the function returns an error message
```

```
  seqconfint(as.AGST(pT, iD, sT, sTo=list(T=2, z=1.7)), type="so")

## End(Not run)
```

---

typeIerr *type I error rate of a GSD*

Description

typeIerr is a function that computes the type I error rate of a GSD.

Usage

```
typeIerr(GSD)
```

Arguments

GSD	object of the class GSTobj or list with the following elements: K = number of stages, a = vector with futility boundaries (not supported yet), b = rejection boundaries, t = vector with information fractions; see example blow.

Value

typeIerr returns the type I error rate of a GSD.

Author(s)

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References

O'Brien, PC, Fleming, TR (1979) "A multiple testing procedure for clinical trials", *Biometrics*, 35 , 549-556

Schoenfeld, D (2001) "A simple Algorithm for Designing Group Sequential Clinical Trials", *Biometrics*, 27, 972-974

See Also

GSTobj

Examples

```
##The following calculates the type I error rate of a GSD.

GSD <- list(K=4,a=rep(-8,4),b=c(4.333,2.963,2.359,2.014),
t=c(0.25,0.5,0.75,1),Imax=0.22)

typeIerr(GSD)
```

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