

Package ‘gsrsb’

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Type Package

Title Group Sequential Refined Secondary Boundary

Version 1.2.1

Description A gate-keeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. Computations related to group sequential primary and secondary boundaries. Refined secondary boundaries are calculated for a gate-keeping test on a primary and a secondary endpoint in a group sequential design with multiple interim looks. The choices include both the standard boundaries and the boundaries using error spending functions.

See Tamhane et al. (2018), "A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks", *Biometrics*, 74(1), 40-48.

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cdBoundary	<i>Lower and Upper Bounds Generator</i>
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Description

Generate lower and upper bounds for programs calculating the secondary endpoint's type I error when the correlation rho between the primary endpoint and the secondary endpoint equals 1.

Usage

```
cdBoundary(cvec, dvec, gammaVec, dlt, upper = TRUE)
```

Arguments

cvec	primary boundary.
dvec	secondary boundary.
gammaVec	square root of information vector.
dlt	test statistic of the primary endpoint follows a normal distribution with mean dlt and standard deviation 1.
upper	type of bounds, upper bound is TRUE, lower bound is FALSE.

Details

This function generates upper and lower bounds for further computation. For more details, refer to Tamhane et al. (2018, Biometrics), section 4.2.

Value

lower and upper bounds for programs calculating the secondary endpoint's type I error when the correlation rho is 1.

Author(s)

Jiangtao Gou

References

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74(1), 40-48. Gou, J. (2022). Sample size optimization and initial allocation of the significance levels in group sequential trials with multiple endpoints. *Biometrical Journal*, 64(2), 301-311.

Examples

```
cvec <- rep(1.992, 3)
dvec <- c(1.535*sqrt(3), 1.535*sqrt(3/2), 1.535)
gammaVec <- c(sqrt(1/3), sqrt(2/3), 1)
dlt <- 2
uBoundary <- cdBoundary(cvec, dvec, gammaVec, dlt, upper=TRUE)
```

genCorrMat

Correlation Matrix Generator

Description

Generate correlation matrix between standardized sample mean test statistics for the two endpoint at different looks.

Usage

```
genCorrMat(gammaVec, type, rhoPS = 0)
```

Arguments

gammaVec	a vector which contains $\gamma_1, \dots, \gamma_{K-1}, \gamma_K$, square root of information vector.
type	type of primary or secondary endpoint. For primary endpoint calculation, type is 1, the returned matrix is K by K. For secondary endpoint calculation, type is 2, the returned matrix is (K+1) by (K+1).
rhoPS	correlation between primary and secondary endpoints.

Details

This function generates correlation matrix between different mean statistics. For more details, refer to Tamhane et al. (2018, *Biometrics*), section 2.

Value

correlation matrix, K by K for primary endpoint, (K+1) by (K+1) for secondary endpoint, where K is the number of interims.

Author(s)

Jiangtao Gou

Fengqing (Zoe) Zhang

References

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74(1), 40-48. Tamhane, A. C., & Gou, J. (2022). Chapter 2 - Multiple test procedures based on p-values. In X. Cui, T. Dickhaus, Y. Ding, & J. C. Hsu (Eds.), *Handbook of multiple comparisons* (Vol. 45, pp. 11–34).

Examples

```
corrMat <- genCorrMat(gammaVec=c(sqrt(1/3), sqrt(2/3), 1), type=2, rhoPS = 0.3)
```

initLocPeak

Find the Location of Maximum, Standard OBF and POC

Description

Calculate the location of maximal type I error of the standard O'Brien-Fleming and Pocock refined secondary boundaries.

Usage

```
initLocPeak(alpha, tVec, cvec, type = 2, initIntvl = c(1, 4))
```

Arguments

alpha	type I error.
tVec	information vector.
cvec	primary group sequential boundary.
type	type of the test procedure for the secondary endpoint. O'Brien- Fleming (OBF) type error spending function is 1, Pocock (POC) type error spending function is 2.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function search the location of the maximal point, in order to calculate the standard (original) O'Brien-Fleming (OBF) and Pocock (POC) refined secondary boundaries.

Value

location of maximum, a number between 1 and the number of interims

Author(s)

Jiangtao Gou

References

O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.

Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191-199.

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

See Also

SecondaryBoundary, ldInitLocBeak

Examples

```
require(mvtnorm)
K <- 8
gammaVec <- sqrt((1:K)/K)
tVec <- gammaVec^2
alpha <- 0.025
c <- 2.072274
cvec <- c/gammaVec
loc <- ldInitLocPeak(alpha, tVec, cvec, type=2, initIntvl=c(1,3))
```

ldInitLocPeak

Find the Location of Maximum, Error Spending Approach

Description

Calculate the location of maximal type I error of secondary endpoint.

Usage

```
ldInitLocPeak(alpha, tVec, cvec, type = 2, initIntvl = c(0.8, 4))
```

Arguments

alpha	type I error.
tVec	information vector.
cvec	primary group sequential boundary.
type	type of the test procedure for the secondary endpoint. O'Brien- Fleming (OBF) type error spending function is 1, Pocock (POC) type error spending function is 2.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function searches the location of maximal type I error of secondary endpoint by using the error spending approach.

Value

location of maximum, a number between 1 and the number of interims.

Author(s)

Jiangtao Gou

References

- Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, **74**, 40-48.

See Also

ldSecondaryBoundary, initLocBeak

Examples

```
## Not run:
require(mvtnorm)
require(ldbounds)
K <- 6;
tVec <- c(140,328,453,578,659,1080)/1080;
alpha = 0.025;
cvec.obf <- ldbounds::ldBounds(tVec,iuse=c(1),alpha=c(alpha),sides=1);
cvec <- cvec.obf$upper.bounds;
loc <- ldInitLocPeak(alpha,tVec,cvec,type=2,initIntvl=c(0.9,4))

## End(Not run)
```

 ldNominalSig

 Calculate Nominal Significance, Error Spending Approach

Description

Nominal significance for the secondary endpoint are calculated by using the error spending approach.

Usage

```
ldNominalSig(alpha, tVec, cvec, locPeak, type = 2, initIntvl = c(1, 4))
```

Arguments

alpha	original significance level.
tVec	information vector.
cvec	primary group sequential boundary.
locPeak	location of maximum, a number between 1 and the number of interims.
type	O'Brien- Fleming (OBF) type error spending function is 1, Pocock (POC) type error spending function is 2.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function calculates the nominal significance level of any Lan-DeMets error spending boundary. The original significance level is used to choose the initial searching range of the nominal significance.

Value

nominal significance of the secondary group sequential boundary.

Author(s)

Jiangtao Gou

References

Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, **74**, 40-48.

See Also

nominalSig, secondaryBoundaryVecLD

Examples

```
## Not run:
require(mvtnorm)
require(ldbounds)
K <- 6;
tVec <- c(140,328,453,578,659,1080)/1080;
alpha <- 0.025;
cvec.obf <- ldbounds::ldBounds(t=tVec,iuse=c(1),alpha=c(alpha),sides = 1);
cvec <- cvec.obf$upper.bounds;
alphaprime <- ldNominalSig(alpha,tVec,cvec,locPeak=4,type=2,
  initIntvl=c(1,4))

## End(Not run)
```

 ldPrimaryBoundary

Calculate Primary Boundaries, the Error Spending Approach

Description

Primary boundaries calculation of Lan-DeMets OBF and POC.

Usage

```
ldPrimaryBoundary(tVec, alpha, type = 1, initIntvl = c(0.8, 8))
```

Arguments

tVec	a vector of information, $\gamma\text{Vec} = \sqrt{t\text{Vec}}$.
alpha	significance level
type	type of sequential procedure. OBF is 1, POC is 2.
initIntvl	parameter for function uniroot (two numbers)

Value

a vector of primary boundaries.

Author(s)

Jiangtao Gou

References

- Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, *74*(1), 40-48.
- Gou, J. (2023). Trigger strategy in repeated tests on multiple hypotheses. *Statistics in Biopharmaceutical Research*, *15*(1), 133–140.

See Also

primaryBoundary

ldSecControl	<i>Difference between the Error Rate and Significance Level, the Error Spending Approach</i>
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Description

Calculate the difference between the error rate and significance level for the secondary endpoint, Lan-DeMets error spending approach.

Usage

```
ldSecControl(ap, alpha, cvec, tVec, ExtrmLoc, type = 2)
```

Arguments

ap	significance level for the primary endpoint
alpha	targeted significance level for the secondary endpoint
cvec	a vector of calculated primary boundaries
tVec	a vector of information, $\gamma\text{Vec} = \sqrt{t\text{Vec}}$
ExtrmLoc	an integer between 1 and K, locate the maximum of type I error of secondary endpoint
type	type of sequential procedures. Type 1 OBF d, Type 2 POC d.

Value

difference between alpha and the calculated error rate.

Author(s)

Jiangtao Gou

References

- Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74(1), 40-48.

See Also

secControl

ldSecondaryBoundary *Calculate Refined Secondary Boundary, Error Spending Approach*

Description

Refined secondary boundaries are calculated by using the error spending approach.

Usage

```
ldSecondaryBoundary(
  alpha,
  tVec,
  cvec,
  locPeak,
  type = 2,
  initIntvl = c(0.6, 4)
)
```

Arguments

alpha	original significance level.
tVec	information vector.
cvec	primary group sequential boundary.
locPeak	location of maximum, a number between 1 and the number of interims.
type	type of the test procedure for the secondary endpoint. O'Brien- Fleming (OBF) type error spending function is 1, Pocock (POC) type error spending function is 2.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function calculates the refined secondary boundaries of any Lan-DeMets error spending boundary based on the primary boundaries.

Value

refined secondary boundaries.

Author(s)

Jiangtao Gou

References

Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, *74*, 40-48.

See Also

secondaryBoundary, secondaryBoundaryVecLD

Examples

```
## Not run:
require(mvtnorm)
require(ldbounds)
K <- 6;
tVec <- c(140,328,453,578,659,1080)/1080;
alpha = 0.025;
cvec.obf <- ldbounds::ldBounds(t=tVec,iuse=c(1),alpha=c(alpha),sides = 1);
cvec <- cvec.obf$upper.bounds;
secbound <- ldSecondaryBoundary(alpha,tVec,cvec,locPeak=4,type=2,
  initIntvl=c(0.8,8))

## End(Not run)
```

nominalSig

Calculate Nominal Significance, Standard Approach

Description

Nominal significance for the secondary endpoint are calculated by using the standard (original) approach.

Usage

```
nominalSig(gammaVec, cvec)
```

Arguments

gammaVec square root of information.
cvec group sequential boundary.

Details

This function calculates the nominal significance level of any given boundary.

Value

nominal significance

Author(s)

Jiangtao Gou

References

- O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.
- Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191-199.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, *74*, 40-48.

See Also

ldNominalSig, secondaryBoundaryVecOrig

Examples

```
require(mvtnorm)
require(ldbounds)
nSig <- nominalSig(gammaVec=c(sqrt(1/3),1),cvec=c(2.2,1.8))
```

primaryBoundary

Calculate Primary Boundaries, Standard Approach

Description

Primary boundaries calculation of standard (original) OBF and POC.

Usage

```
primaryBoundary(gammaVec, alpha, type = 1, initIntvl = c(1, 4))
```

Arguments

gammaVec	a vector of square root of information.
alpha	significance level
type	type of sequential procedure. OBF is 1, POC is 2.
initIntvl	parameter for function uniroot (two numbers)

Value

original OBF and POC boundaries (primary endpoints) (a number, $c_{\cdot}(K)$).

Author(s)

Jiangtao Gou

References

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

See Also

ldPrimaryBoundary

primaryBoundaryVec *Calculate the Primary Boundaries*

Description

Primary boundaries are calculated, including the standard approach and the error spending approach.

Usage

```
primaryBoundaryVec(  
  alpha,  
  tVec,  
  OBF = TRUE,  
  LanDeMets = FALSE,  
  digits = 2,  
  printOut = TRUE,  
  initIntvl = c(1, 8)  
)
```

Arguments

alpha	significance level for the primary endpoint.
tVec	information (vector).
OBF	type of procedures. TRUE for OBF, FALSE for POC.
LanDeMets	type of procedures. TRUE for Lan-Demets type boundaries, FALSE for original boundaries.
digits	number of digits for output,
printOut	TRUE for printing the boundaries.
initIntvl	parameter for function uniroot (two numbers) for function primaryBoundary or function ldPrimaryBoundary

Value

OBF and POC boundaries (primary endpoints) (vector).

Author(s)

Jiangtao Gou

References

- Jennison, C. and Turnbull, B. W. (2000). *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC, New York.
- Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.
- O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.
- Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191-199.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74(1), 40-48.

Examples

```
require(mvtnorm)
K <- 4
alpha <- 0.025
tVec <- (1:K)/K
boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,4),
  OBF=TRUE,LanDeMets=FALSE,digits=3,printOut=TRUE)
boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,4),
  OBF=FALSE,LanDeMets=FALSE,digits=3,printOut=TRUE)
boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,8),
  OBF=TRUE,LanDeMets=TRUE,digits=3,printOut=TRUE)
boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,4),
  OBF=FALSE,LanDeMets=TRUE,digits=3,printOut=TRUE)
```

`psbTeXtable`*Summarize Primary and Refined Secondary Boundaries in a TeX table*

Description

Primary boundaries and refined secondary boundaries are listed in a TeX table.

Usage

```
psbTeXtable(  
  alpha,  
  tVec,  
  pOBF = TRUE,  
  sOBF = FALSE,  
  LanDeMets = FALSE,  
  digits = 2  
)
```

Arguments

<code>alpha</code>	type I error probability.
<code>tVec</code>	vector of relative information levels. The last element in the vector is 1.
<code>pOBF</code>	type of primary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
<code>sOBF</code>	type of secondary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
<code>LanDeMets</code>	type of boundary, TRUE is the error spending approach, FALSE is the original approach.
<code>digits</code>	number of digits after decimal point to display in the table.

Details

This function gives a TeX format table including both primary boundary and refined secondary boundary. The number of digits after decimal point can be specified through parameter `digits`.

Value

a TeX format table including both primary boundary and refined secondary boundary.

Author(s)

Jiangtao Gou

Fengqing (Zoe) Zhang

References

- Glimm, E., Maurer, W., and Bretz, F. (2010). Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* **29**, 219-228.
- Hung, H. M. J., Wang, S.-J., and O'Neill, R. (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *Journal of Biopharmaceutical Statistics* **17**, 1201-1210.
- Jennison, C. and Turnbull, B. W. (2000). *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC, New York.
- Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.
- O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.
- Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191-199.
- Tamhane, A. C., Mehta, C. R., and Liu, L. (2010). Testing a primary and a secondary endpoint in a group sequential design. *Biometrics* **66**, 1174-1184.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74, 40-48.

Examples

```
require(mvtnorm)
require(ldbounds)
require(xtable)
psbTeXtable(alpha=0.025, tVec=c(1/2, 3/4, 1), pOBF=TRUE, sOBF=FALSE, LanDeMets=FALSE)
```

refinedBoundary	<i>Summarize Primary and Refined Secondary Boundaries, Nominal Significance</i>
-----------------	---

Description

Primary boundaries, refined secondary boundaries, and nominal significance for the secondary endpoint are listed.

Usage

```
refinedBoundary(
  alpha,
  tVec,
  pOBF = TRUE,
  sOBF = FALSE,
  LanDeMets = FALSE,
  digits = 2
)
```


Arguments

alpha	type I error probability.
tVec	vector of relative information levels. The last element in the vector is 1.
pOBF	type of primary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
sOBF	type of secondary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
LanDeMets	type of boundary, TRUE is the error spending approach, FALSE is the original approach.
digits	number of digits after decimal point for primary and secondary boundaries.

Details

This function gives a list including primary boundary, refined secondary boundary, and the nominal significance for the secondary endpoint. The number of digits for the nominal significance depends on parameter alpha.

Value

a result list including primary boundary, refined secondary boundary, and the nominal significance for the secondary endpoint.

Author(s)

Jiangtao Gou

References

- Glimm, E., Maurer, W., and Bretz, F. (2010). Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* **29**, 219-228.
- Hung, H. M. J., Wang, S.-J., and O'Neill, R. (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *Journal of Biopharmaceutical Statistics* **17**, 1201-1210.
- Jennison, C. and Turnbull, B. W. (2000). *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC, New York.
- Lan, K. K. G., and Demets, D. L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika* **70**, 659-663.
- O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.
- Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191-199.
- Tamhane, A. C., Mehta, C. R., and Liu, L. (2010). Testing a primary and a secondary endpoint in a group sequential design. *Biometrics* **66**, 1174-1184.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74, 40-48

Examples

```
require(mvtnorm)
require(ldbounds)
result <- refinedBoundary(alpha=0.05,tVec=c(0.2,0.6,1))
result$primaryBoundary
result$secondaryBoundary
result$nomialSignificance
```

secControl	<i>Difference between the Error Rate and Significance Level, Standard Approach</i>
------------	--

Description

Calculate the difference between the error rate and significance level for the secondary endpoint, standard (original) approach.

Usage

```
secControl(d, alpha, cvec, gammaVec, ExtrmLoc, type = 2)
```

Arguments

d	boundary of secondary endpoint at the final look (a number, $d_{(K)}$)
alpha	targeted significance level for the secondary endpoint
cvec	a vector of calculated primary boundaries
gammaVec	square root of information
ExtrmLoc	an integer between 1 and K, locate the maximum of type I error of secondary endpoint
type	type of sequential procedures. Type 1 OBF d, Type 2 POC d.

Value

difference between alpha and the calculated error rate.

Author(s)

Jiangtao Gou

References

Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74(1), 40-48.

See Also

ldSecControl

 secondaryBoundary *Calculate the Refined Secondary Boundaries, Standard OBF and POC*

Description

Calculate the standard O'Brien-Fleming and Pocock refined secondary boundaries

Usage

```
secondaryBoundary(alpha, tVec, cvec, locPeak, type = 2, initIntvl = c(1, 4))
```

Arguments

alpha	type I error.
tVec	information vector.
cvec	primary group sequential boundary.
locPeak	location of maximum, a number between 1 and the number of interims.
type	type of the test procedure for the secondary endpoint. O'Brien- Fleming (OBF) type error spending function is 1, Pocock (POC) type error spending function is 2.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function calculates the standard (original) O'Brien-Fleming (OBF) and Pocock (POC) refined secondary boundaries.

Value

standard O'Brien-Fleming and Pocock refined secondary boundaries.

Author(s)

Jiangtao Gou

References

- O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.
- Pocock, S. J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika* **64**, 191-199.
- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74, 40-48.

See Also

ldSecondaryBoundary, initLocBeak

Examples

```
## Not run:
require(mvtnorm)
K <- 8
gammaVec <- sqrt((1:K)/K)
tVec <- gammaVec^2
alpha = 0.025
c <- 2.072274
cvec <- c/gammaVec
loc <- initLocPeak(alpha, tVec, cvec, type=2, initIntvl=c(1,4))
sbvec <- secondaryBoundary(alpha, tVec, cvec, loc, type=2,
  initIntvl=c(1,8))

## End(Not run)
```

secondaryBoundaryVec *Calculate Refined Secondary Boundaries and Nominal Significance*

Description

Refined secondary boundaries, and nominal significance for the secondary endpoint are calculated.

Usage

```
secondaryBoundaryVec(
  alpha,
  tVec,
  pOBF = TRUE,
  sOBF = FALSE,
  LanDeMets = FALSE,
  initIntvl = c(0.8, 8)
)
```

Arguments

alpha	type I error probability.
tVec	vector of relative information levels. The last element in the vector is 1.
pOBF	type of primary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
sOBF	type of secondary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.

LanDeMets	type of boundary, TRUE is the error spending approach, FALSE is the original approach.
initIntvl	computing paramter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function gives a list including refined secondary boundary and the nominal significance for the secondary endpoint. There are a computing parameter `initIntvl`. Parameter `initIntvl` contains the end-points of the interval to be searched for the root. For Lan-DeMets error spending approach, the lower end point should choose a number slightly less than 1, and the upper end point should choose a number between 4 and 10.

Value

a result list including refined secondary boundary and the nominal significance for the secondary endpoint.

Author(s)

Jiangtao Gou

References

- Glimm, E., Maurer, W., and Bretz, F. (2010). Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* **29**, 219-228.
- Hung, H. M. J., Wang, S.-J., and O'Neill, R. (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *Journal of Biopharmaceutical Statistics* **17**, 1201-1210.
- Jennison, C. and Turnbull, B. W. (2000). *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC, New York.
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- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74, 40-48.

See Also

secondaryBoundaryVecLD, secondaryBoundaryVecOrig

Examples

```
require(mvtnorm)
require(ldbounds)
result <- secondaryBoundaryVec(alpha=0.025, tVec=c(1/2, 1), pOBF=TRUE, sOBF=FALSE,
  LanDeMets=FALSE, initIntvl=c(0.8, 5))
result$secondaryBoundary
result$nomialSignificance
```

secondaryBoundaryVecLD

*Calculate Refined Secondary Boundaries and Nominal Significance,
the Error Spending Approach*

Description

Lan-DeMets refined secondary boundaries, and nominal significance for the secondary endpoint are calculated by using the error spending approach.

Usage

```
secondaryBoundaryVecLD(
  alpha,
  tVec,
  primaryOBF = TRUE,
  secondaryOBF = FALSE,
  initIntvl = c(0.8, 8)
)
```

Arguments

alpha	type I error probability.
tVec	vector of relative information levels. The last element in the vector is 1.
primaryOBF	type of primary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
secondaryOBF	type of secondary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function uses the Lan-DeMets error spending approach, and gives a list including refined secondary boundary and the nominal significance for the secondary endpoint. There is a computing parameter `initIntvl`. Parameter `initIntvl` contains the end-points of the interval to be searched for the root. For Lan-DeMets error spending approach, the lower end point should choose a number slightly less than 1, and the upper end point should choose a number between 4 and 10.

Value

a result list including Lan-DeMets refined secondary boundary and the nominal significance for the secondary endpoint.

Author(s)

Jiangtao Gou

References

- Glimm, E., Maurer, W., and Bretz, F. (2010). Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* **29**, 219-228.
- Hung, H. M. J., Wang, S.-J., and O'Neill, R. (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *Journal of Biopharmaceutical Statistics* **17**, 1201-1210.
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See Also

secondaryBoundaryVec, secondaryBoundaryVecOrig

Examples

```
require(mvtnorm)
require(ldbounds)
result <- secondaryBoundaryVecLD(alpha=0.025,tVec=c(1/2,1),primaryOBF=TRUE,
  secondaryOBF=FALSE,initIntvl=c(0.8,6))
result$secondaryBoundary
result$nomialSignificance
```

 secondaryBoundaryVecOrig

*Calculate Refined Secondary Boundaries and Nominal Significance,
Standard Approach*

Description

Standard refined secondary boundaries, and nominal significance for the secondary endpoint are calculated by using the standard (original) approach.

Usage

```
secondaryBoundaryVecOrig(
  alpha,
  tVec,
  primaryOBF = TRUE,
  secondaryOBF = FALSE,
  initIntvl = c(1, 8)
)
```

Arguments

alpha	type I error probability.
tVec	vector of relative information levels. The last element in the vector is 1.
primaryOBF	type of primary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
secondaryOBF	type of secondary boundary, TRUE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
initIntvl	computing parameter, a pair of numbers containing the end-points of the interval to be searched for the root.

Details

This function uses the standard approach (O'Brien and Fleming 1979, Pocock 1977), and gives a list including refined secondary boundary and the nominal significance for the secondary endpoint. There is a computing parameter `initIntvl`. Parameter `initIntvl` contains the end-points of the interval to be searched for the root. The lower end point should choose a number around 1, and the upper end point should choose a number between 4 and 10.

Value

a result list including standard refined secondary boundary and the nominal significance for the secondary endpoint.

Author(s)

Jiangtao Gou

References

- Glimm, E., Maurer, W., and Bretz, F. (2010). Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine* **29**, 219-228.
- Hung, H. M. J., Wang, S.-J., and O'Neill, R. (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *Journal of Biopharmaceutical Statistics* **17**, 1201-1210.
- Jennison, C. and Turnbull, B. W. (2000). *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC, New York.
- O'Brien, P. C., and Fleming, T. R. (1979). A multiple testing procedure for clinical trials. *Biometrics* **35**, 549-556.
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- Tamhane, A. C., Gou, J., Jennison, C., Mehta, C. R., and Curto, T. (2018). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, 74, 40-48.

See Also

secondaryBoundaryVec, secondaryBoundaryVecLD

Examples

```
require(mvtnorm)
require(ldbounds)
result <- secondaryBoundaryVecOrig(alpha=0.025, tVec=c(1/2,1), primaryOBF=TRUE,
  secondaryOBF=FALSE, initIntvl=c(1,4))
result$secondaryBoundary
result$nomialSignificance
```

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