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Type Package

Title Group Sequential Refined Secondary Boundary

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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. Version 1.0.0 was released on April 12, 2017. See Tamhane et al. (2017+) ``A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks", Biometrics, to appear.

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`cdBoundary` *Lower and Upper Bounds Generator*

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. (2017+), 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. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

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), ..., 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. (2017+), 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. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

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 tyep I error of the standard O'Brien-Fleming and Pocock refined secondary boundaries.

Usage

```
initLocPeak(alpha, tVec, cvec, type = 2, initIntvl = c(1, 4),
  initNrep = 10)
```

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 funciton is 1, Pocock (POC) type error spending funciton is 2.
initIntvl	computing paramter, a pair of numbers containing the end-points of the interval to be searched for the root.
initNrep	computing paramter, number of replica.

Details

This function search the location of the maximal point, in order to calculate the standard (origiinal) 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. (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

`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 <- initLocPeak(alpha,tVec,cvec,type=2,initIntvl=c(1,3),
#      initNrep=1)
```

`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),
  initNrep = 10)
```

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 funciton is 1, Pocock (POC) type error spending funciton is 2.
initIntvl	computing paramter, a pair of numbers containing the end-points of the interval to be searched for the root.
initNrep	computing paramter, number of replica.

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. (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

ldSecondaryBoundary, initLocBeak

Examples

```
#require(mvtnorm)
#require(ldbounds)
#K <- 6;
#tVec <- c(140,328,453,578,659,1080)/1080;
#alpha = 0.025;
#cvec.obf <- bounds(tVec,iuse=c(1),alpha=c(alpha));
#cvec <- cvec.obf$upper.bounds;
#loc <- ldInitLocPeak(alpha,tVec,cvec,type=2,initIntvl=c(0.9,4),initNrep=1)
```

`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),
  nRep = 20)
```

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 funciton is 1, Pocock (POC) type error spending funciton is 2.
`initIntvl`	computing paramter, a pair of numbers containing the end-points of the interval to be searched for the root.
`nRep`	computing paramter, number of replica.

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. (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

nominalSig, secondaryBoundaryVecLD

Examples

```
#require(mvtnorm)
#require(ldbounds)
#K <- 6;
#tVec <- c(140,328,453,578,659,1080)/1080;
#alpha = 0.025;
#cvec.obf <- bounds(tVec,iuse=c(1),alpha=c(alpha));
#cvec <- cvec.obf$upper.bounds;
#alphaprime <- ldNominalSig(alpha,tVec,cvec,locPeak=4,type=2,
#      initIntvl=c(1,4),nRep=1)
```

---

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, gammaVec = sqrt(tVec).
alpha	significance level
type	type of sequential procedure. OBF is 1, POC is 2.
initIntvl	paramter 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. (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

primaryBoundary

---

ldSecControl *Difference between the Error Rate and Significance Level, the Error Spending Approach*

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, gammaVec = sqrt(tVec)
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. (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

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), nRep = 10)
```

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 funciton is 1, Pocock (POC) type error spending funciton is 2.
`initIntvl`	computing paramter, a pair of numbers containing the end-points of the interval to be searched for the root.
`nRep`	computing paramter, number of replica.

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*, to appear.

See Also

secondaryBoundary, secondaryBoundaryVecLD

Examples

```
#require(mvtnorm)
#require(ldbounds)
#K <- 6;
#tVec <- c(140,328,453,578,659,1080)/1080;
#alpha = 0.025;
#cvec.obf <- bounds(tVec,iuse=c(1),alpha=c(alpha));
#cvec <- cvec.obf$upper.bounds;
#secbound <- ldSecondaryBoundary(alpha,tVec,cvec,locPeak=4,type=2,
#    initIntvl=c(0.8,8),nRep=1)
```

---

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 he 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. (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

`ldNominalSig`, `secondaryBoundaryVecOrig`

Examples

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

`p.adjust.gtxr` *Adjust P-values for Multiple Test Procedures*

Description

Given a set of p-values, returns adjusted p-values, including the hybrid Hochberg–Hommel procedure (Gou et al., 2014).

Usage

```
p.adjust.gtxr(p, method = "gtxr", n = length(p))
```

Arguments

`p`	vector of p-values.
`method`	multiplicity correction method, "gtxr" is the hybrid Hochberg–Hommel method, other methods include: "gtxr", "holm", "hochberg", "hommel", "bonferroni", "BH", "BY","fdr", "none".
`n`	number of p-values.

Details

#

Given a set of p-values, returns p-values adjusted using one of several methods. The default method is "gtxr". Other adjustment methods have been included in function p.adjust in R package stats.

Value

a vector of corrected p-values.

Author(s)

Jiangtao Gou

References

Gou, J., Tamhane, A. C., Xi, D., and Rom. D. (2014). A class of improved hybrid Hochberg-Hommel type step-up multiple test procedures. *Biometrika* **101**, 899-911.

See Also

`p.adjust`

Examples

```
pvalues.raw <- c(0.002,0.007,0.005,0.024,0.022,0.009,0.007,0.036,0.060,0.035)
p.adj <- p.adjust.gtxr(pvalues.raw, method = "gtxr")
```

`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`	paramter for function uniroot (two numbers)

Value

original OBF and POC boundaries (primary endpoints) (a number, c_(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, nRep = 100,
  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.
`nRep`	number of replica
`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. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

Examples

```
#require(mvtnorm)
#K = 4
#alpha = 0.025
#tVec = (1:K)/K
#boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,4),
#   OBF=TRUE,LanDeMets=FALSE,nRep=1,digits=3,printOut=TRUE)
#boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,4),
#   OBF=FALSE,LanDeMets=FALSE,nRep=1,digits=3,printOut=TRUE)
#boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,8),
#   OBF=TRUE,LanDeMets=TRUE,nRep=1,digits=3,printOut=TRUE)
#boundaryVector <- primaryBoundaryVec(alpha,tVec,initIntvl=c(1,4),
#   OBF=FALSE,LanDeMets=TRUE,nRep=1,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,
  SpeedQuality = "fast", 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, TURE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
sOBF	type of secondary boundary, TURE 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.
SpeedQuality	quality-speed tradeoff parameter. Choices are fastest, fast, acceptable, normal, good, and stable.
digits	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. When the choice of parameter SpeedQuality is fastest, fast, acceptable, or normal, the default number of digits is 2. When the choice of parameter SpeedQuality is good or stable, the default number of digits is 2. The number of digits after decimal point can also 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. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

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` *Summarize Primary and Refined Secondary Boundaries, Nominal Significance*

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,
  SpeedQuality = "fast", 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, `TURE` is the O'Brien-Fleming boundary, `FALSE` is the Pocock boundary.
`sOBF`	type of secondary boundary, `TURE` 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.
`SpeedQuality`	quality-speed tradeoff parameter. Choices are `fastest`, `fast`, `acceptable`, `normal`, `good`, and `stable`.
`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. When the choice of parameter `SpeedQuality` is `fastest`, `fast`, `acceptable`, or `normal`, the default number of digits for boundaries is 2. When the choice of parameter `SpeedQuality` is `good` or `stable`, the default number of digits for boundaries is 2. The number of digits for boundaries after decimal point can also be specified through parameter `digits`. 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. (2017+). A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks. *Biometrics*, to appear.

Examples

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

secControl *Difference between the Error Rate and Significance Level, Standard Approach*

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. (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

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),
  nRep = 10)
```

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 funciton is 1, Pocock (POC) type error spending funciton is 2.
`initIntvl`	computing paramter, a pair of numbers containing the end-points of the interval to be searched for the root.
`nRep`	computing paramter, number of replica.

Details

This function calculates the standard (origiinal) 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*, to appear.

See Also

ldSecondaryBoundary, initLocBeak

Examples

```
#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),
#      initNrep=1)
#sbvec <- secondaryBoundary(alpha,tVec,cvec,loc,type=2,
#       initIntvl=c(1,8),nRep=1)
```

---

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, nRepVec = c(10, 10, 10, 10), 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, TURE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
sOBF	type of secondary boundary, TURE 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.
nRepVec	computing paramter, number of replica, a vector of four numbers.
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 two computing parameters `nRepVec` and `initIntvl`. Parameter `nRepVec` includes four numbers: `nRepVec[1]` is the number of replica for calculating primary boundaries, `nRepVec[2]` is the number of replica for searching the location of peak, `nRepVec[3]` is the number of replica for calculating secondary boundaries, `nRepVec[4]` is the number of replica for calculating the nominal significance. 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.

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. (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

`secondaryBoundaryVecLD`, `secondaryBoundaryVecOrig`

Examples

```
#require(mvtnorm)
#require(ldbounds)
#result <- secondaryBoundaryVec(alpha=0.025,tVec=c(1/2,1),pOBF=TRUE,sOBF=FALSE,
#       LanDeMets=FALSE,nRepVec=c(1,1,1,1),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,
  nRepVec = c(10, 10, 10, 10), 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, `TURE` is the O'Brien-Fleming boundary, `FALSE` is the Pocock boundary.
`secondaryOBF`	type of secondary boundary, `TURE` is the O'Brien-Fleming boundary, `FALSE` is the Pocock boundary.
`nRepVec`	computing paramter, number of replica, a vector of four numbers.
`initIntvl`	computing paramter, 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 are two computing parameters `nRepVec` and `initIntvl`. Parameter `nRepVec` includes four numbers: `nRepVec[1]` is the number of replica for calculating primary boundaries, `nRepVec[2]` is the number of replica for searching the location of peak, `nRepVec[3]` is the number of replica for calculating secondary boundaries, `nRepVec[4]` is the number of replica for calculating the nominal significance. 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.

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. (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

`secondaryBoundaryVec`, `secondaryBoundaryVecOrig`

Examples

```
#require(mvtnorm)
#require(ldbounds)
#result <- secondaryBoundaryVecLD(alpha=0.025,tVec=c(1/2,1),primaryOBF=TRUE,
#        secondaryOBF=FALSE, nRepVec=c(1,1,1,1),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, nRepVec = c(10, 10, 10, 10), 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, TURE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
secondaryOBF	type of secondary boundary, TURE is the O'Brien-Fleming boundary, FALSE is the Pocock boundary.
nRepVec	computing paramter, number of replica, a vector of four numbers.
initIntvl	computing paramter, 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 are two computing parameters nRepVec and initIntvl. Parameter nRepVec includes four numbers: nRepVec[1] is the number of replica for calculating primary boundaries, nRepVec[2] is the number of replica for searching the location of peak, nRepVec[3] is the number of replica for calculating secondary boundaries, nRepVec[4] is the number of replica for calculating the nominal significance. 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.

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. (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

`secondaryBoundaryVec`, `secondaryBoundaryVecLD`

Examples

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

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