# Package: gsrsb (via r-universe)

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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.

**License** GPL-3

**Encoding** UTF-8

**Depends** R (>= 4.2.0)

**Imports** stats (>= 4.0.0), mvtnorm (>= 1.1.0), ldbounds (>= 2.0.0), xtable (>= 1.8.0)

**RoxygenNote** 7.2.3

**NeedsCompilation** no

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**Repository** CRAN

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## Contents

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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. (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), ..., 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 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))
```

## 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. |

## 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. (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 <- initLocPeak(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 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. |

## 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 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. |

## 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, 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. (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` *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. (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 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. |

## 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 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. (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 | 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,
  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

| | |
|---|---|
| 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. |
| 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. 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` *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,
  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. |
| 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` *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. (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 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. |

## 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*, 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, 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. |
| 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.

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.

## 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, `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. |
| `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 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.

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.

## 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, `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. |
| `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 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.

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.

## 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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