Package 'esDesign'

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Type Package

Title Adaptive Enrichment Designs with Sample Size Re-Estimation

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Author Zhao Yang, Ruitao Lin, Guosheng Yin and Ying Yuan

Maintainer Zhao Yang <yangz98@connect.hku.hk>

Description Software of 'esDesign' is developed to implement the adaptive enrichment designs with sample size re-estimation presented in Lin et al. (2021) <doi:10.1016/j.cct.2020.106216>. In details, three-proposed trial designs are provided, including the AED1-SSR (or ES1-SSR), AED2-SSR (or ES2-SSR) and AED3-SSR (or ES3-SSR). In addition, this package also contains several widely used adaptive designs, such as the Marker Sequential Test (MaST) design proposed Freidlin et al. (2014) <doi:10.1177/1740774513503739>, the adaptive enrichment designs without early stopping (AED or ES), the sample size re-estimation procedure (SSR) based on the conditional power proposed by Proschan and Hunsberger (1995), and some useful functions. In details, we can calculate the futility and/or efficacy stopping boundaries, the sample size required, calibrate the value of the threshold of the difference between subgroup-specific test statistics, conduct the simulation studies in AED, SSR, AED1-SSR, AED2-SSR and AED3-SSR.

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`AED.boundary` *Calculate the critical value used at the final analysis in AED*

Description

`AED.boundary()` is used to calculate the critical value used at the final analysis in AED design, meanwhile preserving the overall type I error rate at α level

Usage

```
AED.boundary(rho, alpha, Info, epsilon)
```

Arguments

`rho`	The proportion of subgroup 1
`alpha`	The overall type I error rate
`Info`	The infromation fraction
`epsilon`	The threshold of difference between the subgroup-specific test statistics

Value

The critical value used at the final analysis

References

- Lin, R., Yang, Z., Yuan, Y. and Yin, G., 2021. Sample size re-estimation in adaptive enrichment design. Contemporary Clinical Trials, 100, p.106216. <doi: 10.1016/j.cct.2020.106216>

Examples

```
AED.boundary(rho = 0.5, alpha = 0.05, Info = 0.5, epsilon = 0.5)
```

`AED.sim` *Conduct the simulation studies of the Adaptive Enrichment Design without early stopping boundary*

Description

The `AED.sim()` is used to conduct the simulation studies of the Adaptive Enrichment Design without early stopping boundary. The AED design is quite similar with the AED1_SSR design. But, in the AED design, the futility stopping boundary and the Sample Size Re-estimation Procedure are removed. On the contrary, a fixed sample size is used to replace the sample size re-estimated procedure. In addition, an ϵ-rule is also introduced to select the subgroup with larger subgroup-specific test statistic.

Usage

```
AED.sim(
  N1,
  N2,
  rho,
  alpha,
  beta,
  theta,
  theta0,
  K,
  Info,
  epsilon,
  sigma0,
  nSim,
  Seed
)
```

Arguments

`N1`	The sample size used at the first stage
`N2`	The sample size used at the second stage
`rho`	The proportion of the subgroup 1
`alpha`	The overall Type I error rate
`beta`	The (1 - Power)

theta	The sizes of treatment effects in subgroups 1 and 2 among the experimental arm
theta0	The size of treatment effect in standard arm
K	The number of subgroups
Info	The observed information
epsilon	The threshold of difference between the subgroup-specific test statistics
sigma0	The variance of the treatment effect
nSim	The number of simulated studies
Seed	The random Seed

Value

A list contains

- nTotal The average expected sample size
- H00 The probability of rejecting the null hypothesis of H_{00}
- H01 The probability of rejecting the null hypothesis of H_{01}
- H02 The probability of rejecting the null hypothesis of H_{02}
- H0 The probabilities of rejecting at least one of the null hypothesis
- Enrich01 The prevalence of adaptive enrichment of subgroup 1
- Enrich02 The prevalence of adaptive enrichment of subgroup 2

References

- Lin, R., Yang, Z., Yuan, Y. and Yin, G., 2021. Sample size re-estimation in adaptive enrichment design. Contemporary Clinical Trials, 100, p.106216. <doi: 10.1016/j.cct.2020.106216>

Examples

```
N1 <- 310
N2 <- 310
rho <- 0.5
alpha <- 0.05
beta <- 0.20
theta <- c(0,0)
theta0 <- 0
K <- 2
Info <- 0.5
epsilon <- 0.5
sigma0 <- 1
nSim <- 1000
Seed <- 6
AED.sim(N1 = N1, N2 = N2, rho = rho, alpha = alpha,
        beta = beta, theta = theta, theta0 = theta0,
        K  = K, Info = Info, epsilon = epsilon,
        sigma0 = sigma0, nSim = nSim, Seed = Seed)
```

AED1_SSR.boundary *Calculate the critical value used at the final analysis of the Adaptive Enrichment Design (Strategy 1) with Sample Size Re-estimation Procedure*

Description

The AED1_SSR.boundary() is used to calculate the critical value required at the final analysis of the Adaptive Enrichment Design (Strategy 1) with sample size re-estimation procedure. In the AED1-SSR design, the adaptive enrichment strategy is guided by a pre-specified futility stopping boundary and a threshold of the difference between the subgroup-specific test statistics.

Usage

```
AED1_SSR.boundary(rho, alpha, pstar, Info, epsilon)
```

Arguments

rho	The proportion of subgroup 1.
alpha	The overall Type I error rate.
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
Info	The observation information, which is commonly calculated through the sample size used at each stage of the trial.
epsilon	The threshold of the difference between subgroup-specific test statistics.

References

- Lin, R., Yang, Z., Yuan, Y. and Yin, G., 2021. Sample size re-estimation in adaptive enrichment design. Contemporary Clinical Trials, 100, p.106216. <doi: 10.1016/j.cct.2020.106216>

Examples

```
AED1_SSR.boundary(rho = 0.5, alpha = 0.05, pstar = 0.2, Info = 0.5, epsilon = 0.5)
```

AED1_SSR.CP *Calculate the conditional power of the Adaptive Enrichment Design with (Strategy 1) Sample Size Re-estimation Procedure*

Description

The AED1_SSR.CP() is used to calculate the conditional power of the Adaptive Enrichment Design (Strategy 1) with sample size re-estimation procedure

Usage

```
AED1_SSR.CP(c, Z1, N1, N2)
```

Arguments

c	The critical value used at the final analysis
Z1	The test statistic obtained at the interim analysis
N1	The sample size used at the first stage
N2	The sample size used at the second stage

Value

A list contains

- Critical.Value The critical value used at the final analysis
- Conditional.Power The value of conditional power given the observed data

References

- Lin, R., Yang, Z., Yuan, Y. and Yin, G., 2021. Sample size re-estimation in adaptive enrichment design. Contemporary Clinical Trials, 100, p.106216. <doi: 10.1016/j.cct.2020.106216>

Examples

```
c <- 2.258
Z1 <- 1.975
N1 <- 248
N2 <- 200
AED1_SSR.CP(c = 2.258, Z1 = 1.974, N1 = 248, N2 = 200)
```

AED1_SSR.N2 *Calculate the sample size required at the second stage of the adaptive enrichment design (Strategy1) with Sample Size Re-estimation Procedure*

Description

The `AED1_SSR.N2()` is used to calculated the sample size required at the second stage of the Adaptive Enrichment Design (Strategy 1) with Sample Size Re-estimation Procedure.

Usage

```
AED1_SSR.N2(c, z1, N1, beta)
```

Arguments

c	The critical value used at the final analysis
z1	The test statistic obtained at the interim analysis
N1	The sample size used at the first stage
beta	The (1 - power)

Value

The Value of the re-estimated sample size

References

- Lin, R., Yang, Z., Yuan, Y. and Yin, G., 2021. Sample size re-estimation in adaptive enrichment design. Contemporary Clinical Trials, 100, p.106216. <doi: 10.1016/j.cct.2020.106216>

Examples

```
c <- 2.258
z1 <- 1.974
N1 <- 248
beta <- 0.2
AED1_SSR.N2(c = c, z1 = z1, N1 = N1, beta = beta)
```

AED1_SSR.sim — *Conduct the simulation studies of the Adaptive Enrichment Design (Strategy 1) with Sample Size Re-estimation Procedure*

Description

The AED1_SSR.sim() is used to conduct the simulation study of the Adaptive Enrichment Design (Strategy 1) with Sample Size Re-estimation procedure

Usage

```
AED1_SSR.sim(
  N1,
  rho,
  alpha,
  beta,
  pstar,
  theta,
  theta0,
  Info,
  K = 2,
  epsilon,
  sigma0,
```

```
  nSim,
  Seed
)
```

Arguments

N1	The sample size used at the first stage
rho	The proportion of subgroup 1 among the overall patients
alpha	The overall Type I error rate
beta	The (1 - Power)
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
theta	The sizes of the treatment effect in subgroups 1 and 2 with the experimental arm
theta0	The size of the treatment effect in standard arm
Info	The observation information
K	The number of subgroups. The default value is K = 2
epsilon	The threshold of the difference between the subgroup-specific test statistic
sigma0	The variance of the treatment effect
nSim	The number of simulated studies
Seed	The random seed

Value

A list contains

- nTotal The average expected sample size
- H00 The probability of rejecting the null hypothesis of H_{00}
- H01 The probability of rejecting the null hypothesis of H_{01}
- H02 The probability of rejecting the null hypothesis of H_{02}
- H0 The probabilities of rejecting at least one of the null hypothesis
- ESF The probability of early stopping for futility
- ESE The probability of early stopping for efficacy
- Enrich01 The prevalence of adaptive enrichment of subgroup 1
- Enrich02 The prevalence of adaptive enrichment of subgroup 2

References

- Lin, R., Yang, Z., Yuan, Y. and Yin, G., 2021. Sample size re-estimation in adaptive enrichment design. Contemporary Clinical Trials, 100, p.106216. <doi: 10.1016/j.cct.2020.106216>

Examples

```
res <- AED1_SSR.sim(
  N1 = 310, rho = 0.5,
  alpha = 0.05, beta = 0.2, pstar = 0.2,
  theta = c(0,0), theta0 = 0, Info = 0.5,
  epsilon = 0.5, sigma0 = 1, nSim = 1000, Seed = 6)
```

AED2_SSR.boundary *Calculate the futility and efficacy stopping boundaries of the Adaptive Enrichment Design (Strategy 2) with Sample Size Re-estimation Procedure*

Description

The AED2_SSR.boundary() is used to calculate the futility and efficacy stopping boundaries of the Adaptive Enrichment Design (strategy 2) with Sample Size Re-estimation Procedure. In the AED2-SSR design, an ϵ-rule is introduced to select the subgroup with larger test statistic. In practice, the value of ϵ should be calibrated to fit the requirement of the trial.

Usage

```
AED2_SSR.boundary(rho, alpha, pstar, epsilon)
```

Arguments

rho	The proportion of subgroup 1
alpha	The overall Type I error rate
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
epsilon	The threshold of difference between the subgroup-specific test statistics

Value

A list contains

- upper.boundary The upper and efficacy stopping boundary
- lower.boundary The lower and futility stopping boundary

Examples

```
rho <- 0.5
alpha <- 0.05
pstar <- 0.15
epsilon <- 0.5
AED2_SSR.boundary(rho = rho, alpha = alpha, pstar = pstar, epsilon = epsilon)
```

AED2_SSR.CP *Calculate the $N2$ and the critical value C in the Adaptive Enrichment Design (Strategy 2) with Sample Size Re-estimation Procedure*

Description

The AED2_SSR.CP() is used to calculate the sample size required at the second stage and the critical value used at the final analysis in the Adaptive Enrichment Design with Sample Size Re-estimation Procedure. In addition, this function can also used to conduct the conditional power analysis in terms of $N2$

Usage

```
AED2_SSR.CP(
  Z1 = NULL,
  delta = NULL,
  N1 = NULL,
  pstar,
  rho,
  epsilon,
  alpha,
  beta,
  N2 = NULL
)
```

Arguments

Z1	The test statistic obtained at the interim analysis
delta	The standardized size of treatment effect, which can be estimated by using $(\mu_X - \mu_Y)/\sqrt{\sigma^2}$.
N1	The sample size used at the first stage
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
rho	The proportion of subgroup 1
epsilon	The threshold of the difference between subgroup-specific test statistics.
alpha	The overall Type I error rate
beta	The (1 -Power)
N2	The pre-specified sample size used at the second stage, which is used to conduct the conditional power analysis

Value

A list contains

- upper.boundary The efficacy stopping boundary
- lower.boundary The futility stopping boundary

- N2 The pre-specified sample size used at the second stage, which is used to implement the conditional power analysis
- Conditional.Power The value of conditional power given the value of N2 in the conditional power analysis
- P.Value The corresponding P-Value used at the final analysis in the conditional power analysis
- N2.CP The re-estimated sample size of N2 to ensure an adequate conditional power
- c.CP The estimated the critical value used at the final analysis based the conditional power

Examples

```
Z1 <- 1.974
delta <- 0.355
N1 <- 248
pstar <- 0.15
alpha <- 0.05
rho <- 0.5
epsilon <- 0.5
beta <- 0.20
N2 <- 104
res <- AED2_SSR.CP(Z1 = Z1, delta = delta, N1 = N1, pstar = pstar,
           alpha = alpha, rho = rho, epsilon = epsilon,
           beta = beta, N2 = N2)
```

AED2_SSR.sim — *Conduct the simulation studies of the Adaptive Enrichment Design (Strategy 2) with Sample Size Re-estimation Procedure*

Description

The AED2_SSR.sim() is used to conduct the simulation studies of the Adaptive Enrichment Design (Strategy) with sample size re-estimation procedure. The AED2-SSR is different from the AED3-SSR, in which an ϵ-rule is introduced to select the subgroup with larger subgroup-specific test statistic.

Usage

```
AED2_SSR.sim(
  N1,
  rho,
  alpha,
  beta,
  pstar,
  theta,
  theta0,
  sigma0,
  epsilon,
```

```
  nSim,
  Seed
)
```

Arguments

N1	The sample size used in the first stage
rho	The proportion of subgroup 1
alpha	The overall Type I error rate
beta	The (1 - power)
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
theta	The sizes of treatment effect in subgroups 1 and 2 with the experimental treatment
theta0	The size of treatment effect with the standard treatment
sigma0	The variance of the treatment effect
epsilon	The threshold of the difference between subgroup-specific test statistics
nSim	The number of simulated studies
Seed	The random seed

Value

A list contains

- nTotal The average expected sample size
- H00 The probability of rejecting the null hypothesis of H_{00}
- H01 The probability of rejecting the null hypothesis of H_{01}
- H02 The probability of rejecting the null hypothesis of H_{02}
- H0 The probabilities of rejecting at least one of the null hypothesis
- ESF The probability of early stopping for futility
- ESE The probability of early stopping for efficacy
- Enrich01 The prevalence of adaptive enrichment of subgroup 1
- Enrich02 The prevalence of adaptive enrichment of subgroup 2
- Trigger03 The prevalence of no enrichment

Examples

```
N <- 310
rho <- 0.5
alpha <- 0.05
beta <- 0.2
theta <- c(0,0)
theta0 <- 0
sigma0 <- 1
epsilon <- 0.5
```

```
pstar <- 0.20
nSim <- 1000
Seed <- 6
res <- AED2_SSR.sim(N1 = N, rho = rho, alpha = alpha,
             beta = beta, theta = theta, theta0 = theta0,
             sigma0 = sigma0, pstar = pstar, epsilon = epsilon,
             nSim = nSim, Seed = Seed)
```

`AED3_SSR.boundary` *Calculate the futility and efficacy stopping boundaries in Adaptive enrichment design (Strategy 3) with Sample Size Re-estimation Procedure for the continuous endpoint*

Description

The `AED3_SSR.boundary()` is used to calculate the futility and efficacy stopping boundaries in the Adaptive Enrichment Design with Sample Size Re-estimation Procedure.

Usage

```
AED3_SSR.boundary(rho, alpha, pstar)
```

Arguments

`rho`	The proportion of subgroup 1
`alpha`	The overall Type I error rate
`pstar`	The `(1 -power)` of accepting the null hypothesis at the interim analysis.

Value

A list contains

- upper.boundary The upper or the efficacy stopping boundary
- lower.boundary The lower or the futility stopping boundary

Examples

```
rho <- 0.5
alpha <- 0.05
pstar <- 0.15
res <- AED3_SSR.boundary(rho = rho, alpha = alpha, pstar = pstar)
```

AED3_SSR.CP *Calculate the $N2$ and the critical value C in the Adaptive Enrichment Design (Strategy 3) with Sample Size Re-estimation Procedure*

Description

The AED3_SSR.CP() is used to calculate the sample size required at the second stage and the critical value used at the final analysis in the Adaptive Enrichment Design with Sample Size Re-estimation Procedure. In addition, this function can also used to conduct the conditional power analysis in terms of $N2$

Usage

```
AED3_SSR.CP(
  Z1 = NULL,
  delta = NULL,
  N1 = NULL,
  pstar,
  rho,
  alpha,
  beta,
  N2 = NULL
)
```

Arguments

Z1	The test statistic obtained at the interim analysis
delta	The standardized size of treatment effect, which can be estimated by using $(\mu_X - \mu_Y)/\sqrt{\sigma^2}$.
N1	The sample size used at the first stage
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
rho	The proportion of subgroup 1
alpha	The overall Type I error rate
beta	The (1 -Power)
N2	The pre-specified sample size used at the second stage, which is used to conduct the conditional power analysis

Value

A list contains

- N2 The pre-specified sample size used at the second stage, which is used to implement the conditional power analysis
- Conditional.Power The value of conditional power given the value of N2 in the conditional power analysis

- P.Value The corresponding P-Value used at the final analysis in the conditional power analysis
- N2.CP The re-estimated sample size of N2 to ensure an adequate conditional power
- c.CP The estimated the critical value used at the final analysis based the conditional power

Examples

```
Z1 <- 1.974
delta <- 0.355
N1 <- 248
pstar <- 0.15
alpha <- 0.05
rho <- 0.5
beta <- 0.20
N2 <- 108
AED3_SSR.CP(Z1 = Z1, delta = delta, N1 = N1, pstar = pstar,
           alpha = alpha, rho = rho, beta = beta, N2 = N2)
```

`AED3_SSR.sim` *Conduct the simulation studies of the Adaptive Enrichment Design (Strategy 3) with Sample Size Re-estimation Procedure based on Futility and Efficacy Stopping Boundaries for the continuous endpoint*

Description

The `AED3_SSR.sim()` is used to conduct the adaptive enrichment design with Sample Size Re-estimation, in which futility and efficacy stopping boundaries are used to guide the adaptive enrichment process. For the adaptively enriched subgroup, we re-estimate the sample size to maintain an adequate conditional power meanwhile protect the overall Type I error rate.

Usage

```
AED3_SSR.sim(N1, rho, alpha, beta, theta, theta0, sigma0, pstar, nSim, Seed)
```

Arguments

`N1`	The sample size used at the first stage
`rho`	The proportion of subgroup 1 among the overall patients
`alpha`	The overall Type I error rate
`beta`	The `(1 -Power)`
`theta`	The sizes of treatment effect in subgroups 1 and 2 with experimental treatment
`theta0`	The size of treatment effect in standard treatment
`sigma0`	The known variance of the treatment effect
`pstar`	The `(1 -power)` of accepting the null hypothesis at the interim analysis.
`nSim`	The number of simulated studies.
`Seed`	The random seed

Value

A list contains

- nTotal The average expected sample size
- H00 The probability of rejecting the null hypothesis of H_{00}
- H01 The probability of rejecting the null hypothesis of H_{01}
- H02 The probability of rejecting the null hypothesis of H_{02}
- H0 The probabilities of rejecting at least one of the null hypothesis
- Enrich01 The prevalence of adaptive enrichment of subgroup 1
- Enrich02 The prevalence of adaptive enrichment of subgroup 2
- Trigger03 The prevalence of early stopping for the situation, in which the treatment effect in subgroup 1 is superiority, while the treatment effect in subgroup 2 is inconclusive
- Trigger04 The prevalence of early stopping for the situation, in which the treatment effect in subgroup 2 is superiority, while the treatment effect in subgroup 2 is inconclusive
- ESF The probability of early stopping for futility
- ESE The probability of early stopping for efficacy

Examples

```
N <- 310
rho <- 0.5
alpha <- 0.05
beta <- 0.2
theta <- c(0,0)
theta0 <- 0
sigma0 <- 1
pstar <- 0.20
nSim <- 100
Seed <- 6
res <- AED3_SSR.sim(N1 = N, rho = rho, alpha = alpha,
             beta = beta, theta = theta, theta0 = theta0,
             sigma0 = sigma0, pstar = pstar, nSim = nSim,
             Seed = Seed)
```

`MaST.sim` *Conduct the simulation studies of the Marker Sequential Test design*

Description

The `MaST.sim()` is used to conduct the simulation studies of the marker sequential test design (MaST).

Usage

```
MaST.sim(N, rho, alpha, beta, theta, theta0, sigma0, nSim, Seed)
```

Arguments

N	The total sample size used at the trial
rho	The proportion of subgroup 1 among the overall patients
alpha	The overall Type I error rate
beta	The (1 - Power)
theta	The sizes of treatment effect in subgroups 1 and 2 with the experimental arm
theta0	The size of treatment effect in the standard arm
sigma0	The variance of the treatment effect
nSim	The number of simulated studies
Seed	The random seed

Value

A list contains

- nTotal The average expected sample size
- H00 The probability of rejecting the null hypothesis of H_{00}
- H01 The probability of rejecting the null hypothesis of H_{01}
- H02 The probability of rejecting the null hypothesis of H_{02}
- H0 The probabilities of rejecting at least one of the null hypothesis

References

- Freidlin, B., Korn, E. L., and Gray, R. (2014). Marker sequential test (MaST) design. Clinical trials, 11(1), 19-27. <doi:10.1177/1740774513503739>

Examples

```
N <- 310
rho <- 0.5
alpha <- 0.05
beta <- 0.20
theta <- c(0,0)
theta0 <- 0
sigma0 <- 1
nSim <- 1000
Seed <- 6
MaST.sim(N = N, rho = rho, alpha = alpha, beta = beta,
         theta = theta, theta0 = theta0, sigma0 = sigma0,
         nSim = nSim, Seed = Seed)
```

SD.sim *Conduct the simulation studies of the standard design*

Description

The SD.sim() is used to implement the simulation studies of the standard design.

Usage

```
SD.sim(N, rho, alpha, beta, theta, theta0, sigma0, nSim, Seed)
```

Arguments

N	The total sample size required
rho	The proportion of subgroup 1
alpha	The overall Type I error rate
beta	The (1 -Power)
theta	The sizes of treatment effects for subgroups 1 and 2 in experimental arm
theta0	The size of treatment effect for the control arm
sigma0	The variance of the treatment effect
nSim	The number of simulated studies
Seed	The random seed

Value

A list contains,

- nTotal the total sample used
- The power of the specified trial. Here, the power is defined as the probability of rejecting the null hypothesis.

Examples

```
N <- 620
rho <- 0.5
alpha <- 0.05
beta <- 0.2
theta <- c(0.2,0.0)
theta0 <- 0
sigma0 <- 1
nSim <- 1000
Seed <- 6
SD.sim(N = N, rho = rho,
       alpha = alpha, beta = beta, theta = theta, theta0 = theta0,
       sigma0 = sigma0, nSim = nSim, Seed = Seed)
```

SigP *Commonly used α-spending functions*

Description

The SigP() is used to calculate the reduced significant level based on several widely used α-spending functions, such as the "Pocock", "Lan-DeMets", "O'Brein-Fleming" and "Power" functions.

Usage

```
SigP(alpha, Info, esFunction = "Pocock", gamma = 1)
```

Arguments

alpha	The overall Type I error rate
Info	The fraction of the observed information
esFunction	The specific α-spending function. For example, esFunction = "Pocock" for the Pocock method, esFunction = "LD" for the Lan-Demets method, esFunction = "OF" for the O'Brein-Fleming method, and esFunction = "Power" for the Power method.
gamma	The parameter used in the Power method. The default value is gamma = 1.

Value

The reduced significant level

Examples

```
alpha <- 0.05
Info <- 0.5
esFunction = "OF"
SigP(alpha = alpha, Info = Info, esFunction = esFunction)
```

---

sSize.norm *Sample size calculation for the standard design with continuous endpoint*

Description

The sSize.norm() is used to calculate the sample size used in the standard design with continuous endpoint.

Usage

```
sSize.norm(alpha, beta, theta, side, r, sigma2)
```

Arguments

alpha	The Type I error rate or the significant level
beta	beta The (1 -Power)
theta	The size of treatment effect
side	One-sided or two-sided Test
r	The ratio of sample size between the experimental and control arms
sigma2	The variance of the treatment effect

Value

A list contains the total sample size, and the sample sizes required for the experimental and control arms.

Examples

```
alpha <- 0.05
beta <- 0.2
theta <- 0.2
side <- 1
r <- 1
sigma2 <- 0.8
sSize.norm(alpha = alpha, beta = beta, theta = theta,
side = side, r = r, sigma2 = sigma2)
```

SSR.boundary *Calculate the futility and efficacy stopping boundaries for Sample Size Re-estimation Procedure based on the conditional error function*

Description

The SSD.boundary() is used to calculate the futility and efficacy stopping boundaries, meanwhile protect the overall Type I error rate at the pre-specified level.

Usage

```
SSR.boundary(alpha, pstar)
```

Arguments

alpha	The overall Type I error rate
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.

Value

A list contain

- upper.boundary The efficacy stopping boundary at the interim analysis
- lower.boundary The futility stopping boundary at the interim analysis

References

- Proschan MA, Hunsberger SA. Designed extension of studies based on conditional power. Biometrics 1995:1315-24. <doi:10.2307/2533262>

Examples

```
alpha <- 0.05
pstar <- 0.2
res <- SSR.boundary(alpha = alpha, pstar = pstar)
```

SSR.CP *Calculate the $N2$ and the critical value C in Sample Size Re-estimation Procedure*

Description

The `SSR.CP()` is used to calculate the sample size required at the second stage and the critical value used at the final analysis. In addition, this function can also used to conduct the conditional power analysis in terms of $N2$

Usage

```
SSR.CP(Z1 = NULL, delta = NULL, N1 = NULL, pstar, alpha, beta, N2 = NULL)
```

Arguments

`Z1`	The test statistic obtained at the interim analysis
`delta`	The standardized size of treatment effect, which can be estimated by using $(\mu_X - \mu_Y)/\sqrt{\sigma^2}$.
`N1`	The sample size used at the first stage
`pstar`	The `(1 -power)` of accepting the null hypothesis at the interim analysis.
`alpha`	The overall Type I error rate
`beta`	The `(1 -Power)`
`N2`	The pre-specified sample size used at the second stage, which is used to conduct the conditional power analysis

Value

A list contains

- N2 The pre-specified sample size used at the second stage, which is used to implement the conditional power analysis
- Conditional.Power The value of conditional power given the value of N2 in the conditional power analysis
- P.Value The corresponding P-Value used at the final analysis in the conditional power analysis
- N2.CP The re-estimated sample size of N2 to ensure an adequate conditional power
- c.CP The estimated the critical value used at the final analysis based the conditional power

References

- Proschan MA, Hunsberger SA. Designed extension of studies based on conditional power. Biometrics 1995:1315-1324. <doi:10.2307/2533262>

Examples

```
Z1 <- 1.527
delta <- 0.137
N1 <- 248
pstar <- 0.15
alpha <- 0.05
beta <- 0.2
res <- SSR.CP(Z1 = Z1, delta = delta, N1 = N1,
       pstar = pstar, alpha = alpha, beta = beta)
```

SSR.sim *Conduct the simulation studies using SSR*

Description

The SSR.sim() is used to implement the simulation studies based on the Sample Size Re-estimation Procedure.

Usage

```
SSR.sim(N, rho, alpha, beta, theta, theta0, sigma0, pstar, nSim, Seed)
```

Arguments

N	The sample size used at the first stage. Note that this N is not the initial total sample size calculated using the standard design
rho	The proportion of subgroup 1
alpha	The overall Type I error rate

beta	The (1 -Power)
theta	The sizes of treatment effects for subgroups 1 and 2 in the experimental arm
theta0	The size of treatment effect in the control arm
sigma0	The variance of the treatment effect
pstar	The (1 -power) of accepting the null hypothesis at the interim analysis.
nSim	The number of simulated studies
Seed	The random seed

Value

A list contains

- nTotal The average total sample size used in SSR
- H0 The power of SSR under the specific trial design. Here, the power is defined as the probability of rejecting the null hypothesis
- ESF The percentage of early stopping for futility
- ESE The percentage of early stopping for efficacy

References

- Proschan MA, Hunsberger SA. Designed extension of studies based on conditional power. Biometrics 1995:1315-1324. <doi:10.2307/2533262>

Examples

```
N <- 310
rho <- 0.5
alpha <- 0.05
beta <- 0.2
pstar <- 0.2
theta <- c(0.2,0)
theta0 <- 0
sigma0 <- 1.0
nSim <- 1000
Seed <- 6
res <- SSR.sim(N = N, rho = rho, alpha = alpha, beta = beta, theta = theta,
        theta0 = theta0, sigma0 = sigma0, pstar = pstar,
        nSim = nSim, Seed = Seed)
```

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