Package 'ssMRCT'

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Type Package

Title Regional consistency evaluation and sample size calculation for MRCTs

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Description A comprehensive suite of functions for designing and analyzing Multi-Regional Clinical Trials (MRCTs), featuring sepcialized tools for consistency probability calculation and optimal regional fraction(s) determination. Support extends to both one MRCT (one trial encompassing all regions) and two MRCTs (two pivotal, independent MRCTs) frameworks. Developed for regulatory decision support and trial optimization in global drug development programs.

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Contents

`ssMRCT-package` *Regional consistency evaluation and sample size calculation for MRCTs*

Description

The **ssMRCT** package offers a comprehensive suite of functions for designing and analyzing Multi-Regional Clinical Trials (MRCTs), featuring specialized tools for:

- **Consistency Probability Calculation**: Computes the probability that treatment effects across regions satisfy predefined consistency criteria;
- **Optimal Regional Fraction Determination**: Identifies the ideal regional enrollment proportions to minimize regional sample size while maintaining consistency probability.

Support extends to both *one MRCT* (one trial encompassing all regions) and *two MRCTs* (two pivotal, independent MRCTs) frameworks. Developed for regulatory decision support and trial optimization in global drug development programs.

Functions

Key functions included in the package:

conProb, conProb2 Calculate the (conditional) consistency probability for one/two MRCT(s) with corresponding overall sample size(s).

regFrac, regFrac2 Calculate the optimal regional fraction(s) given the (conditional) consistency probability for one/two MRCT(s), with corresponding overall sample size(s).

References

MHLW (2007). Basic Principles on Global Clinical Trials. https://www.pmda.go.jp/files/000153265.pdf

Kunhai Qing, Xinru Ren, Shuping Jiang, Ping Yang, Menggang Yu and Jin Xu (2025). Regional consistency evaluation and sample size calculation under two MRCTs. http://arxiv.org/abs/2411.15567

`conProb` *Consistency probability for one MRCT via Japan's criterion I (conditional version)*

Description

Calculate the consistency probability for one MRCT via Japan's criterion I (conditional version).

Usage

```
conProb(
  alpha,
  power,
  pi = 0.5,
  rF,
  d,
  sigmaTrt,
```

```
  sigmaCtrl = sigmaTrt,
  randRatio = 1
)
```

Arguments

alpha	The Type I error.
power	Power.
pi	The threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
rF	The regional fraction.
d	The true mean of difference of response.
sigmaTrt	The standard deviation of response in the treatment group.
sigmaCtrl	The standard deviation of response in the control group. Defaults to sigmaTrt.
randRatio	The randomization ratio between the treatment group and control group. Defaults to 1.

Details

The consistency probability via Japan's criterion I (conditional version), $\Pr\left(D_k \geq \pi D \mid T > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{1-\beta}\int_{-z_{1-\beta}}^{\infty} \Phi\left(\frac{(1-\pi)(u+z_{1-\alpha}+z_{1-\beta})}{\sqrt{f_k^{-1}-1}}\right)\phi(u)du.$$

Since there is no closed form of above equation, conProb utilizes the integrate function for numerical integration.

As the first equation includes none of d, sigmaTrt, sigmaCtrl and randRatio, if only the consistency probability is considered, then the values of d and sigmaTrt could be arbitrary.

The overall sample size is calculated based on the below equation,

$$N^{(\mathrm{c})} = \frac{\left\{r^{-1}\sigma^{2(\mathrm{t})} + \sigma^{2(\mathrm{c})}\right\}(z_{1-\alpha}+z_{1-\beta})^2}{d^2}, \quad N^{(\mathrm{t})} = rN^{(\mathrm{c})}.$$

Then $N = N^{(\mathrm{t})} + N^{(\mathrm{c})}$. Additionally, both of $N^{(\mathrm{t})}$ and $N^{(\mathrm{c})}$ should be integers and hence N.

Value

A list containing the following two components:

CP The consistency probability, a scalar.

N The overall sample size.

Examples

```
conProb(alpha = 0.05, power = 0.8, rF = 0.271, d = 1, sigmaTrt = 4)
```

conProb2 *Consistency probability for two MRCTs via the extended Japan's criterion I (conditional version)*

Description

Calculate the consistency probability for two MRCTs via the extended Japan's criterion I (conditional version).

Usage

```
conProb2(
  alpha,
  power1,
  power2 = power1,
  pi = 0.5,
  rF1,
  rF2 = rF1,
  d1,
  d2 = d1,
  sigmaTrt1,
  sigmaCtrl1 = sigmaTrt1,
  sigmaTrt2 = sigmaTrt1,
  sigmaCtrl2 = sigmaTrt2,
  randRatio1 = 1,
  randRatio2 = randRatio1
)
```

Arguments

alpha	The Type I error.
power1	Power for MRCT 1.
power2	Power for MRCT 2. Defaults to power1.
pi	The threshold ratio in the extended Japan's criterion I (conditional version). Defaults to 0.5.
rF1	The regional fraction for MRCT 1.
rF2	The regional fraction for MRCT 2. Defaults to rF1.
d1	The true mean of difference of response for MRCT 1.
d2	The true mean of difference of response for MRCT 2. Defaults to d1.
sigmaTrt1	The standard deviation of response in the treatment group for MRCT 1.
sigmaCtrl1	The standard deviation of response in the control group for MRCT 1. Defaults to sigmaTrt1.
sigmaTrt2	The standard deviation of response in the treatment group for MRCT 2. Defaults to sigmaTrt1.
sigmaCtrl2	The standard deviation of response in the control group for MRCT 2. Defaults to sigmaTrt2.
randRatio1	The randomization ratio between the treatment group and control group for MRCT 1.

randRatio2 The randomization ratio between the treatment group and control group for MRCT 2. Defaults to randRatio1.

Details

The extended consistency probability via the extended Japan's criterion I (conditional version), $\Pr\left(D_{k,\text{pool}} \geq \pi D_{\text{pool}} \mid T^{(1)} > z_{1-\alpha}, T^{(2)} > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{(1-\beta_1)(1-\beta_2)} \int_{-z_{1-\beta_1}}^{\infty} \int_{-z_{1-\beta_2}}^{\infty} \Phi\left(\frac{(1-\pi)\left\{w^{(1)}\sigma_d^{(1)}u + w^{(2)}\sigma_d^{(2)}v + w^{(1)}d^{(1)} + w^{(2)}d^{(2)}\right\}}{\sqrt{\left\{\left(f_k^{(1)}\right)^{-1} - 1\right\}\left(w^{(1)}\sigma_d^{(1)}\right)^2 + \left\{\left(f_k^{(2)}\right)^{-1} - 1\right\}\left(w^{(2)}\sigma_d^{(2)}\right)^2}} \right) \phi(u)\phi(v)dudv,$$

where $w^{(s)} = N^{(s)}/(N^{(1)} + N^{(2)})$ and

$$\sigma_d^2 = (D) = \frac{(r+1)\left\{\sigma^{2(\text{t})} + r\sigma^{2(\text{c})}\right\}}{rN}.$$

Since there is no closed forms of above equations, conProb2 utilizes the adaptIntegrate function for numerical integration.

Additionally, if we assume homogeneous variances, equal treatment effects and equal randomization ratios across two studies, i.e., $\sigma^{2(\text{t},1)} = \sigma^{2(\text{t},2)}$, $\sigma^{2(\text{c},1)} = \sigma^{2(\text{c},2)}$, $d^{(1)} = d^{(2)}$ and $r^{(1)} = r^{(2)}$, then the above equation reduces to

$$\frac{1}{(1-\beta_1)(1-\beta_2)} \int_{-(z_{1-\beta_1}+z_{1-\beta_2})/\sqrt{2}}^{\infty} \left[\Phi\left(\frac{(1-\pi)\left\{\sqrt{2}u + (2z_{1-\alpha} + z_{1-\beta_1} + z_{1-\beta_2})\right\}}{\sqrt{\left(f_k^{(1)}\right)^{-1} + \left(f_k^{(2)}\right)^{-1} - 2}} \right) \left\{\Phi\left(u + \sqrt{2}z_{1-\beta_1}\right) + \Phi\left(u + \sqrt{2}z_{1-\beta_2}\right) - 1\right\}\right] \phi(u)du.$$

Since now the above equation includes none of d1=d2, sigmaTrt1=sigmaTrt2, sigmaCtrl1=sigmaCtrl2 randRatio1 = randRatio2, if only the consistency probability is considered, then the values of d1 and sigmaTrt1 could be arbitrary.

The overall sample size is calculated in the same way as conProb. Additionally, both of $N^{(\text{t},s)}$ and $N^{(\text{c},s)}$ should be integers and hence N^s.

Value

A list containing the following two components:

CP The consistency probability, a scalar.

N1 The overall sample size for MRCT 1.

N2 The overall sample size for MRCT 2.

Examples

```
### Remark 7
conProb2(alpha = 0.05, power1 = 0.8, power2 = 0.9, rF1 = 0.141, d1 = 1, sigmaTrt1 = 4)
conProb2(alpha = 0.05, power1 = 0.8, power2 = 0.9, rF1 = 0.100, rF2 = 0.238, d1 = 1, sigmaTrt1 = 4)
### Remark 9
conProb2(alpha = 0.05, power1 = 0.8, rF1 = 0.154, d1 = 1, sigmaTrt1 = 4)
```

---

conProbII *Consistency probability for one MRCT via Japan's criterion II (conditional version)*

Description

Calculate the consistency probability for one MRCT via Japan's criterion II (conditional version).

Usage

```
conProbII(
  alpha,
  power,
  rF,
  d,
  sigmaTrt,
  sigmaCtrl = sigmaTrt,
  pTrt,
  pCtrl,
  randRatio = 1,
  responseType = c("continuous", "binary"),
  B = 1e+05
)
```

Arguments

alpha	The Type I error.
power	Power.
rF	The regional fractions, a K x 1 vector with each component representing the regional fraction in region k and the sum must equal 1.
d	The true mean of difference of response.
sigmaTrt	The standard deviation of response in the treatment group.
sigmaCtrl	The standard deviation of response in the control group. Defaults to sigmaTrt.
pTrt	The mean of the response in the treatment group.
pCtrl	The mean of the response in the control group.
randRatio	The randomization ratio between the treatment group and control group. Defaults to 1.
responseType	The type of response. One of "continuous" and "binary".
B	The number of simulation by Monto Carlo for responseType = "binary". Defaults to 100,000.

Details

The consistency probability via Japan's criterion II (conditional version),

$$\Pr\left(D_k \geq 0, k = 1, \ldots, K \mid T > z_{1-\alpha}\right),$$

is approximately

$$\frac{1}{1-\beta}\int_{-z_{1-\beta}}^{\infty}\prod_{k=1}^{K}\Phi\left(\frac{u + z_{1-\alpha} + z_{1-\beta}}{\sqrt{f_k^{-1}-1}}\right)\phi(u)du.$$

Since there is no closed form of above equation, `conProbII` utilizes the `integrate` function for numerical integration.

As the first equation includes none of `d`, `sigmaTrt`, `sigmaCtrl` and `randRatio`, if only the consistency probability is considered, then the values of `d` and `sigmaTrt` could be arbitrary.

For binary response, the above approximation loses precision under moderate sample size. Hence `conProbII` applies Monto Carlo to calculate the correct consistency probability.

The overall sample size is calculated in the same way as `conProb`. But additionally requiring all of $N_k^{(\mathrm{t})}$ and $N_k^{(\mathrm{c})}$ should be integers and hence $N^{(\mathrm{t})}$, $N^{(\mathrm{c})}$ and N.

Value

A list containing the following two components:

`CP` The consistency probability, a scalar.

`N` The overall sample size.

Examples

```
### Example 1
alpha <- 0.05
power <- 0.8
conProbII(alpha, power, rF = rep(1/2,2), d = 1, sigmaTrt = 4, responseType = "continuous")
conProbII(alpha, power, rF = rep(1/3,3), d = 1, sigmaTrt = 4, responseType = "continuous")
conProbII(alpha, power, rF = rep(1/4,4), d = 1, sigmaTrt = 4, responseType = "continuous")
rFk1 <- 0.101
rFk2 <- rFk3 <- (1-rFk1)/2
rF <- c(rFk1, rFk2, rFk3)
conProbII(alpha, power, rF = rF, d = 1, sigmaTrt = 4, responseType = "continuous")

### Example 2
rFk1 <- 0.149
rFk2 <- rFk3 <- (1-rFk1)/2
rF <- c(rFk1, rFk2, rFk3)
set.seed(123)
conProbII(alpha, power, rF = rF, pTrt = 0.8, pCtrl = 0.7, responseType = "binary")
rFk1 <- 0.14
rFk2 <- rFk3 <- (1-rFk1)/2
rF <- c(rFk1, rFk2, rFk3)
set.seed(123)
conProbII(alpha, power, rF = rF, pTrt = 0.7, pCtrl = 0.6, responseType = "binary")
rFk1 <- 0.101
rFk2 <- rFk3 <- (1-rFk1)/2
rF <- c(rFk1, rFk2, rFk3)
set.seed(123)
```

```
conProbII(alpha, power, rF = rF, pTrt = 0.8, pCtrl = 0.7, responseType = "binary")
conProbII(alpha, power, rF = rF, pTrt = 0.7, pCtrl = 0.6, responseType = "binary")
```

`conProbII2` *Consistency probability for two MRCTs via Japan's criterion II (conditional version)*

Description

Calculate the consistency probability for two MRCTs via Japan's criterion II (conditional version).

Usage

```
conProbII2(
  alpha,
  power1,
  power2 = power1,
  rF1,
  rF2 = rF1,
  d1,
  d2 = d1,
  sigmaTrt1,
  sigmaCtrl1 = sigmaTrt1,
  sigmaTrt2 = sigmaTrt1,
  sigmaCtrl2 = sigmaTrt2,
  pTrt1,
  pCtrl1,
  pTrt2 = pTrt1,
  pCtrl2 = pCtrl1,
  randRatio1 = 1,
  randRatio2 = randRatio1,
  responseType = c("continuous", "binary"),
  B = 1e+05
)
```

Arguments

`alpha`	The Type I error.
`power1`	Power for MRCT 1.
`power2`	Power for MRCT 2. Defaults to `power1`.
`rF1`	The regional fractions for MRCT 1, a `K x 1` vector with each component representing the regional fraction in region k and the sum must equal 1.
`rF2`	The regional fractions for MRCT 2, a `K x 1` vector with each component representing the regional fraction in region k and the sum must equal 1. Defaults to `rF1`.
`d1`	The true mean of difference of response for MRCT 1.
`d2`	The true mean of difference of response for MRCT 2. Defaults to `d1`.
`sigmaTrt1`	The standard deviation of response in the treatment group for MRCT 1.

sigmaCtrl1	The standard deviation of response in the control group for MRCT 1. Defaults to sigmaTrt1.
sigmaTrt2	The standard deviation of response in the treatment group for MRCT 2. Defaults to sigmaTrt1.
sigmaCtrl2	The standard deviation of response in the control group for MRCT 2. Defaults to sigmaTrt2.
pTrt1	The mean of the response in the treatment group for MRCT 1.
pCtrl1	The mean of the response in the control group for MRCT 1.
pTrt2	The mean of the response in the treatment group for MRCT 2. Defaults to pTrt1.
pCtrl2	The mean of the response in the control group for MRCT 2. Defaults to pTrt2.
randRatio1	The randomization ratio between the treatment group and control group for MRCT 1.
randRatio2	The randomization ratio between the treatment group and control group for MRCT 2. Defaults to randRatio1.
responseType	The type of response. One of "continuous" and "binary".
B	The number of simulation by Monto Carlo for responseType = "binary". Defaults to 100,000.

Details

The extended consistency probability via the extended Japan's criterion II (conditional version),

$$\Pr\left(D_{k,\text{pool}} \geq 0, k = 1, \cdots, K \mid T^{(1)} > z_{1-\alpha}, T^{(2)} > z_{1-\alpha}\right),$$

is approximately

$$\frac{1}{(1-\beta_1)(1-\beta_2)} \int_{-z_{1-\beta_1}}^{\infty} \int_{-z_{1-\beta_2}}^{\infty} \prod_{k=1}^{K} \Phi\left(\frac{w^{(1)}\sigma_d^{(1)} u + w^{(2)}\sigma_d^{(2)} v + w^{(1)} d^{(1)} + w^{(2)} d^{(2)}}{\sqrt{\left\{\left(f_k^{(1)}\right)^{-1} - 1\right\}\left(w^{(1)}\sigma_d^{(1)}\right)^2 + \left\{\left(f_k^{(2)}\right)^{-1} - 1\right\}\left(w^{(2)}\sigma_d^{(2)}\right)^2}} \right) \phi(u)\phi(v) du dv,$$

where $w^{(s)}$ and σ_d^2 are defined in conProb2.

Since there is no closed forms of above equations, conProbII2 utilizes the adaptIntegrate function for numerical integration.

For binary response, the above approximation loses precision under moderate sample size. Hence conProbII2 applies Monto Carlo to calculate the correct consistency probability.

The overall sample size is calculated in the same way as conProb. But additionally requiring all of $N_k^{(\text{t},s)}$ and $N_k^{(\text{c},s)}$ should be integers and hence $N^{(\text{t},s)}$, $N^{(\text{c},s)}$ and N^s.

Value

A list containing the following two components:

CP The consistency probability, a scalar.

N1 The overall sample size for MRCT 1.

N2 The overall sample size for MRCT 2.

Examples

```
### Example 3
alpha <- 0.05
power1 <- 0.8
conProbII2(alpha, power1, rF1 = rep(1/2,2), d1 = 1, sigmaTrt1 = 4, responseType = "continuous")
conProbII2(alpha, power1, rF1 = rep(1/3,3), d1 = 1, sigmaTrt1 = 4, responseType = "continuous")
conProbII2(alpha, power1, rF1 = rep(1/4,4), d1 = 1, sigmaTrt1 = 4, responseType = "continuous")
rF11 <- 0.044
rF12 <- rF13 <- (1-rF11)/2
rF1 <- c(rF11, rF12, rF13)
conProbII2(alpha, power1, rF1 = rF1, d1 = 1, sigmaTrt1 = 4, responseType = "continuous")

### Example 4
rF11 <- 0.06
rF12 <- rF13 <- (1-rF11)/2
rF1 <- c(rF11, rF12, rF13)
set.seed(123)
conProbII2(alpha, power1, rF1 = rF1, pTrt1 = 0.8, pCtrl1 = 0.7, responseType = "binary")
rF11 <- 0.044
rF12 <- rF13 <- (1-rF11)/2
rF1 <- c(rF11, rF12, rF13)
set.seed(123)
conProbII2(alpha, power1, rF1 = rF1, pTrt1 = 0.8, pCtrl1 = 0.7, responseType = "binary")
```

`CPlbd` *Lower bound of the consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model.*

Description

Calculate the lower bound of consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model for normal endpoint.

Usage

```
CPlbd(
  alpha,
  beta,
  tau_delta_r,
  delta,
  sigma0r,
  sigma1r,
  fr,
  pi = 0.5,
  randRatio = 1
)
```

Arguments

`alpha`	The one-sided Type I error.
`beta`	The Type II error.

tau_delta_r	The ratio of the standard deviation vs mean of the Gaussian prior for the regional treatment effect.
delta	The mean of the Gaussian prior for the regional treatment effect.
sigma0r	The standard deviation(s) of response in the treatment group for region(s) of interest. A scalar or vector of length equals to the total number of region(s) of interest.
sigma1r	The standard deviation(s) of response in the control group for region(s) of interest. A scalar or vector of length equals to sigma0r.
fr	The regional fraction(s) for the region(s) of interest. A scalar or vector of equal length to sigma0r and sigma1r.
pi	The threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
randRatio	The randomization ratio between the treatment group and control group. Defaults to 1.

Details

The lower bound of the consistency probability via Japan's criterion I (conditional version) under random effects model, $\Pr\left(\widetilde{D}_r \geq \pi\widetilde{D}|T > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{1-\beta}\int_{u>z_\beta}\Phi\left(\frac{2\delta^2(1-\pi)(u+z_{1-\alpha}+z_{1-\beta})}{\tau^2(z_{1-\alpha}+z_{1-\beta})^2}\right)d\Phi(u).$$

provided $\frac{\tau}{\delta} < \frac{\sqrt{2}}{z_{1-\alpha}+z_{1-\beta}}$ Since there is no closed form of above equation, CPlbd utilizes the integrate function for numerical integration.

The sample size(s) for the region(s) of interest at the lower bound are calculated based on solving the below equation for $n_0^{(r)}$,

$$\frac{h_r}{h_r+1} = \frac{\tau^2}{2\delta^2}(z_{1-\alpha}+z_{1-\beta})^2, \quad n_1^{(r)} = \ell n_0^{(r)}$$

where $h_r = \tau^2/\sigma^{2(r)}, \sigma^{2(r)} = \Omega_r/(n_0 f_r), \Omega_r = \ell^{-1}\sigma_1^{2(r)} + \sigma_1^{2(r)}$. Then $n^{(r)} = n_0^{(r)} + n_1^{(r)}$, where both of $n_0^{(r)}$ and $n_1^{(r)}$ should be integers and hence $n^{(r)}$.

Value

A list containing the following components:

CPlbd The lower bound of consistency probability, a scalar.

n0r The regional sample size of the control group. (n.a. when the condition for positive sample size is not met)

n1r The regional sample size of the treatment group. (n.a. when the condition for positive sample size is not met)

nr The regional sample size. (n.a. when the condition for positive sample size is not met)

Examples

```
CPlbd(alpha=0.05, beta=0.2, tau_delta_r=0.4, pi=0.5, delta=0.25, sigma0r=1, sigma1r=1, randRatio=1, fr=c(0.1)
CPlbd(alpha=0.05, beta=0.2, tau_delta_r=0.4, pi=0.5, delta=0.25, sigma0r=c(1,1), sigma1r=c(1,1), randRatio=1,
```

`regFrac` *Regional fraction for one MRCT via Japan's criterion I (conditional version)*

Description

Calculate the minimal regional fraction given the consistency probability for one MRCT via Japan's criterion I (conditional version).

Usage

```
regFrac(
  alpha,
  power,
  pi = 0.5,
  CP = 0.8,
  d,
  sigmaTrt,
  sigmaCtrl = sigmaTrt,
  randRatio = 1
)
```

Arguments

`alpha`	The Type I error.
`power`	Power.
`pi`	The threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
`CP`	the consistency probability. Defaults to 80%.
`d`	The true mean of difference of response.
`sigmaTrt`	The standard deviation of response in the treatment group.
`sigmaCtrl`	The standard deviation of response in the control group. Defaults to `sigmaTrt`.
`randRatio`	The randomization ratio between the treatment group and control group. Defaults to 1.

Details

Given the consistency probability, there is a minimal regional fraction `rF`. To calculate the minimal `rF`, `regFrac` utilizes two core computational components:

- The `conProb` function to compute the (conditional) consistency probability
- The `uniroot` function from the **stats** package for numerical root-finding

The solution is obtained by solving the following equation numerically:

$$\texttt{conProb(rF)} - \texttt{CP} = 0$$
$$\text{where } \texttt{rF} \in (0, 1).$$

The overall sample size is obtain by `conProb` simultaneously.

Value

A list containing the following two components:

`rF` The regional fraction, a scalar.

`N` The overall sample size.

Examples

```
conProb(alpha = 0.05, power = 0.8, rF = 0.271, d = 1, sigmaTrt = 4)

regFrac(alpha = 0.05, power = 0.8, d = 1, sigmaTrt = 4)
```

`regFrac2` *Regional fraction for two MRCTs via the extended Japan's criterion I (conditional version)*

Description

Calculate the optimal regional fractions given the consistency probability for two MRCTs via the extended Japan's criterion I (conditional version).

Usage

```
regFrac2(
  alpha,
  power1,
  power2 = power1,
  pi = 0.5,
  CP = 0.8,
  d1,
  d2 = d1,
  sigmaTrt1,
  sigmaCtrl1 = sigmaTrt1,
  sigmaTrt2 = sigmaTrt1,
  sigmaCtrl2 = sigmaTrt2,
  randRatio1 = 1,
  randRatio2 = randRatio1
)
```

Arguments

`alpha`	The Type I error.
`power1`	Power for MRCT 1.
`power2`	Power for MRCT 2. Defaults to `power1`.
`pi`	The threshold ratio in the extended Japan's criterion I (conditional version). Defaults to 0.5.
`CP`	The consistency probability. Defaults to 80%.
`d1`	The true mean of difference of response for MRCT 1.

d2	The true mean of difference of response for MRCT 2. Defaults to d1.
sigmaTrt1	The standard deviation of response in the treatment group for MRCT 1.
sigmaCtrl1	The standard deviation of response in the control group for MRCT 1. Defaults to sigmaTrt1.
sigmaTrt2	The standard deviation of response in the treatment group for MRCT 2. Defaults to sigmaTrt1.
sigmaCtrl2	The standard deviation of response in the control group for MRCT 2. Defaults to sigmaTrt2.
randRatio1	The randomization ratio between the treatment group and control group for MRCT 1.
randRatio2	The randomization ratio between the treatment group and control group for MRCT 2. Defaults to randRatio1.

Details

Given the consistency probability, there is an optimal pair of regional fractions rF1 and rF2 that minimized the combined region sample size, i.e., $f_k^{(1)}N^{(1)} + f_k^{(2)}N^{(2)}$. Theoretically, the ratio between such rF1 and rF2 is fixed. Hence, regFrac2 utilizes two core computational components:

- The conProb2 function to compute the (conditional) consistency probability for two MRCTs
- The uniroot function from the **stats** package for numerical root-finding

The solution is obtained by solving the following equation numerically:

$$\texttt{conProb2(rF2*k,rF2)} - \texttt{CP} = 0$$
$$\text{where } \texttt{rF2} \in (0, \min(1/k, 1)),$$

where k is the above fixed ratio between rF1 and rF2.

The overall sample size is obtain by conProb2 simultaneously.

Value

A list containing the following two components:

rF1 The regional fraction for MRCT 1, a scalar.

rF2 The regional fraction for MRCT 2, a scalar.

N1 The overall sample size for MRCT 1, an integer.

N2 The overall sample size for MRCT 2, an integer.

Examples

```
### Remark 7
conProb2(alpha = 0.05, power1 = 0.8, power2 = 0.9, rF1 = 0.141, d1 = 1, sigmaTrt1 = 4)

regFrac2(alpha = 0.05, power1 = 0.8, power2 = 0.9, d1 = 1, sigmaTrt1 = 4)

conProb2(alpha = 0.05, power1 = 0.8, power2 = 0.9, rF1=0.1407622, d1 = 1, sigmaTrt1 = 4)
```

`ssCPbinary` *Overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model.*

Description

Calculate the overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model for the binary endpoint.

Usage

```
ssCPbinary(alpha, beta, p0r, p1r, pi = 0.5, randRatio = 1, target, f)
```

Arguments

`alpha`	Type I error for one-sided test.
`beta`	Type II error.
`p0r`	vector of probabilities in the control group. a `R x 1` vector with each component representing the probability in region r.
`p1r`	vector of probabilities in the treatment group. a `R x 1` vector with each component representing the probability in region r.
`pi`	threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
`randRatio`	randomization ratio between the treatment group and control group. Defaults to 1.
`target`	index for the region of interest. an integer of value referring to the region with the corresponding position in `f`.
`f`	vector of regional fractions.a `R x 1` vector with each component representing the fraction in region r and the sum must equal 1.

Details

The overall sample size is calculated based on the below equation,

$$\sum_r \left(\tau^2 + \frac{\Omega_r}{n_0 f_r}\right)^{-1} = \frac{(z_{1-\alpha} + z_{1-\beta})^2}{\delta^2} \quad n_1 = \ell n_0.$$

Since there is no closed form of above equation, `ssCPbinary` utilizes the `uniroot` function for numerical solution for n_0. Then $n = n_0 + n_1$, where both of n_0 and n_1 should be integers and hence n_0.

The consistency probability via Japan's criterion I (conditional version) under random effects model, $\Pr\left(\widetilde{D}_r \geq \pi \widetilde{D} | T > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{1-\beta} \int_{u > z_\beta} \Phi\left(\frac{(1-\pi)(u + z_{1-\alpha} + z_{1-\beta})}{\sqrt{\rho_r^{-1} - 1}}\right) d\Phi(u)$$

where $\rho_r^{-1} - 1 = \frac{h_r}{h_r+1} \sum_{j \neq r}^{R} \frac{h_j}{h_j+1}, w = \frac{1}{\tau^2} \sum_{j=1}^{R} \frac{h_j}{h_j+1}, h_r = \tau^2/\sigma^{2(r)}, \sigma^{2(r)} = \Omega_r/(n_0 f_r)$. Since there is no closed form of above equation, `ssCPbinary` utilizes the `integrate` function for numerical integration.

For the binary endpoint, $\Omega_r = \ell^{-1}\sigma_1^{2(r)} + \sigma_1^{2(r)}, \sigma_1^{2(r)} = p_1^{(r)}(1 - p_1^{(r)}), \sigma_0^{2(r)} = p_0^{(r)}(1 - p_0^{(r)})$. δ and τ are derived based on the naive approach as the mean and standard deviation of the regional risk differences (i.e., $p_1^{(r)} - p_0^{(r)}$).

Value

A list containing the following components:

`n0` The overall sample size of the control group

`n1` The overall sample size of the treatment group

`n` The overall sample size.

`CP` The consistency probability, a scalar.

`"error: condition not met. negative n0 returned"`

`"error: regional fractions do not sum up to 1"` When vector f does not sum up to 1

Examples

```
ssCPbinary(alpha=0.025, beta=0.2, p0r=rep(0.3,3), p1r=c(0.6,0.4,0.2)+rep(0.3,3), pi=0.5, randRatio=1, target=
```

`ssCPnorm` *Overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model.*

Description

Calculate the overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model for the normal endpoint.

Usage

```
ssCPnorm(
  alpha,
  beta,
  delta,
  tau,
  sigma1r,
  sigma0r,
  pi = 0.5,
  randRatio = 1,
  target,
  f
)
```

Arguments

`alpha`	Type I error for one-sided test.
`beta`	Type II error.
`delta`	mean of the Gaussian prior for the regional treatment effect.
`tau`	standard deviation of the Gaussian prior for the regional treatment effect.
`sigma1r`	regional standard deviations of the response in the treatment group, a `R x 1` vector with each component representing the standard deviation in region r .
`sigma0r`	regional standard deviations of the response in the control group. a `R x 1` vector with each component representing the standard deviation in region r.

pi	threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
randRatio	randomization ratio between the treatment group and control group. Defaults to 1.
target	The index for the region of interest. an integer of value referring to the region with the corresponding position in f.
f	regional fractions, a R x 1 vector with each component representing the fraction in region r and the sum must equal 1.

Details

The overall sample size is calculated based on the below equation,

$$\sum_r \left(\tau^2 + \frac{\Omega_r}{n_0 f_r}\right)^{-1} = \frac{(z_{1-\alpha} + z_{1-\beta})^2}{\delta^2} \quad n_1 = \ell n_0.$$

Since there is no closed form of above equation, ssCPnorm utilizes the uniroot function for numerical solution for n_0. Then $n = n_0 + n_1$, where both of n_0 and n_1 should be integers and hence n_0.

The consistency probability via Japan's criterion I (conditional version) under random effects model, $\Pr\left(\widetilde{D}_r \geq \pi\widetilde{D} | T > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{1-\beta}\int_{u>z_\beta} \Phi\left(\frac{(1-\pi)(u + z_{1-\alpha} + z_{1-\beta})}{\sqrt{\rho_r^{-1} - 1}}\right) d\Phi(u)$$

where $\rho_r^{-1} - 1 = \frac{h_r}{h_r+1}\sum_{j\neq r}^{R}\frac{h_j}{h_j+1}, w = \frac{1}{\tau^2}\sum_{j=1}^{R}\frac{h_j}{h_j+1}, h_r = \tau^2/\sigma^{2(r)}, \sigma^{2(r)} = \Omega_r/(n_0 f_r)$. Since there is no closed form of above equation, ssCPnorm utilizes the integrate function for numerical integration.

For the normal endpoint, $\Omega_r = \ell^{-1}\sigma_1^{2(r)} + \sigma_1^{2(r)}$

Value

A list containing the following components:

n0 The overall sample size of the control group

n1 The overall sample size of the treatment group

n The overall sample size.

CP The consistency probability, a scalar.

"error: condition not met. negative n0 returned"

"error: regional fractions do not sum up to 1" When vector f does not sum up to 1

Examples

```
ssCPnorm(alpha=0.025, beta=0.1, delta=0.25, tau=0.1, sigma1r=rep(1,3),sigma0r=rep(1,3), randRatio=1, pi=0.5,
```

ssCPsurvNPH *Overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model.*

Description

Calculate the overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model for the survival endpoint with nPH assumption.

Usage

```
ssCPsurvNPH(
  alpha,
  beta,
  lambda0a,
  lambda0b,
  lambda1a,
  lambda1b,
  breakpoint,
  shape0,
  scale0,
  shape1,
  scale1,
  PW = T,
  unimin,
  unimax,
  pi = 0.5,
  randRatio = 1,
  target,
  f,
  eta
)
```

Arguments

alpha	Type I error for one-sided test.
beta	Type II error.
lambda0a	vector rate parameter of the piece-wise exponential distribution on or before the breakpoint in the control group. a R x 1 vector with each component representing the rate parameter in region r.
lambda0b	vector rate parameter of the piece-wise exponential distribution after the breakpoint in the control group. a R x 1 vector with each component representing the rate parameter in region r.
lambda1a	vector rate parameter of the piece-wise exponential distribution on or before the breakpoint in the treatment group. a R x 1 vector with each component representing the rate parameter in region r.
lambda1b	vector rate parameter of the piece-wise exponential distribution before the breakpoint in the treatment group. a R x 1 vector with each component representing the rate parameter in region r.

breakpoint	scalar of the time at which the hazard changes. Assumed universal breakpoint value across groups and regions.
shape0	vector of the shape parameter of the weibull distribution in the control group (shape=1 reduces to exponential). a R x 1 vector with each component representing the shape parameter in region r.
scale0	vector of the scale parameter of the weibull distribution in the control group (scale=1/rate). a R x 1 vector with each component representing the scale parameter in region r.
shape1	vector of the shape parameter of the weibull distribution in the treatment group(shape=1 reduces to exponential). a R x 1 vector with each component representing the shape parameter in region r.
scale1	vector of the scale parameter of the weibull distribution in the treatment group (scale=1/rate). a R x 1 vector with each component representing the scale parameter in region r.
PW	logical; if TURE (default), survival time follow piece-wise exponential distribution. Otherwise Weibull distribution
unimin	vector of the lower limits of the uniform distribution. a R x 1 vector with each component representing the lower limit in region r.
unimax	vector of the upper limits of the uniform distribution. a R x 1 vector with each component representing the upper parameter in region r.
pi	threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
randRatio	randomization ratio between the treatment group and control group. Defaults to 1.
target	index for the region of interest. an integer of value referring to the region with the corresponding position in f.
f	vector of regional fractions. a R x 1 vector with each component representing the regional fraction in region r and the sum must equal 1.
eta	a scalar of truncated time in RMST. Assumed universal truncated time across groups and regions.

Details

Assume the survival endpoint follows either piece-wise exponential distribution with hazard function (i.e., rate function) $\lambda_k^{(r)} I(0 < t \leq \psi) + \gamma_k^{(r)} I(t > \psi)$, where ψ(breakpoint) is the change point and $\lambda_k^{(r)}$ (lambda0a, lambda0b), $\gamma_k^{(r)}$ (lambda1a, lambda1b) represent the hazard on or before and after the change point ψ in group k of region r. or Weibull distribution (i.e., Weibull($\nu_k^{(r)}, \theta_k^{(r)}$)), with shape parameter $\nu_k^{(r)}$ (shape0,shape1) and scale parameter (i.e., 1/rate parameter) $\theta_k^{(r)}$ (scale0, scale1) for group k region r. Assume the censoring time follows uniform distribution with lower limit unimin and upper limit unimax.

The overall sample size is calculated based on the below equation,

$$\sum_r \left(\tau^2 + \frac{\Omega_r}{n_0 f_r} \right)^{-1} = \frac{(z_{1-\alpha} + z_{1-\beta})^2}{\delta^2} \quad n_1 = \ell n_0.$$

Since there is no closed form of above equation, ssCPsurvPH utilizes the uniroot function for numerical solution for n_0. Then $n = n_0 + n_1$, where both of n_0 and n_1 should be integers and hence n_0.

The consistency probability via Japan's criterion I (conditional version) under random effects model, $\Pr\left(\widetilde{D}_r \geq \pi\widetilde{D}|T > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{1-\beta}\int_{u>z_\beta}\Phi\left(\frac{(1-\pi)(u+z_{1-\alpha}+z_{1-\beta})}{\sqrt{\rho_r^{-1}-1}}\right)d\Phi(u)$$

where $\rho_r^{-1}-1=\frac{h_r}{h_r+1}\sum_{j\neq r}^{R}\frac{h_j}{h_j+1}, w=\frac{1}{\tau^2}\sum_{j=1}^{R}\frac{h_j}{h_j+1}, h_r=\tau^2/\sigma^{2(r)}, \sigma^{2(r)}=\Omega_r/(n_0 f_r)$. Since there is no closed form of above equation, `ssCPsurvPH` utilizes the `integrate` function for numerical integration.

For survival endpoint under non-PH assumption, $\Omega_r=\ell^{-1}\sigma_1^{2(r)}+\sigma_1^{2(r)}$. δ and τ are derived based on the naive approach as the mean and standard deviation of the regional RMST between group difference.

Value

A list containing the following components:

`Dr` regional effect

`sigma2.0r` asymptotic vairance of RMST estimate of the control group in region r

`sigma2.1r` asymptotic vairance of RMST estimate of the treatment group in region r

`n0` The overall sample size of the control group

`n1` The overall sample size of the treatment group

`n` The overall sample size.

`CP` The consistency probability, a scalar.

`"error: condition not met. negative n0 returned"`

`"error: regional fractions do not sum up to 1"` When vector f does not sum up to 1

Examples

```
ssCPsurvNPH(alpha=0.025, beta=0.2,
            lambda0a=c(0.07,0.07,0.07,0.07),lambda0b=c(0.03,0.04,0.05,0.06),
            lambda1a=c(0.02,0.03,0.04,0.05),lambda1b=c(0.03,0.04,0.05,0.06),
            breakpoint=10,
            unimin=rep(0,4),unimax=rep(80*3,4),
            pi=0.5, randRatio=1, target=1, f=rep(1/4,4), eta=80)
```

`ssCPsurvPH` *Overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model.*

Description

Calculate the overall sample size and consistency probability for one MRCT via Japan's criterion I (conditional version) under random effects model for survival endpoint with PH assumption.

Usage

```
ssCPsurvPH(alpha, beta, lambda0r, hr, pi = 0.5, randRatio = 1, target, f, L)
```

Arguments

alpha	one-sided Type I error.
beta	Type II error.
lambda0r	vector of rate parameters in the control group. a R x 1 vector with each component representing the rate parameter in region r.
hr	vector of hazard ratios of treatment group vs control group. a R x 1 vector with each component representing the hr in region r.
pi	threshold ratio in Japan's criterion I (conditional version). Defaults to 0.5.
randRatio	randomization ratio between the treatment group and control group. Defaults to 1.
target	index for the region of interest. an integer of value referring to the region with the corresponding position in f.
f	vector of regional fractions. a R x 1 vector with each component representing the regional fraction in region r and the sum must equal 1.
L	scalar of follow-up time in a study assuming fixed study duration design.

Details

Assume the survival endpoint in region r of group k follows exponential distribution with rate parameter $\lambda_k^{(r)}$: $T_k^{(r)} \sim \exp(\lambda_k^{(r)}), k = 0, 1, r = 1 \dots R$. Assume the censoring time follows uniform distribution with lower limit unimin and upper limit unimax. Assume a study with fixed study duration where each subject is followed for the same length in time (i.e.,L time units) and administrative censoring at the end of study follow-up is the only type of censoring.

The overall sample size is calculated based on the below equation,

$$\sum_r \left(\tau^2 + \frac{\Omega_r}{n_0 f_r}\right)^{-1} = \frac{(z_{1-\alpha} + z_{1-\beta})^2}{\delta^2} \quad n_1 = \ell n_0.$$

Since there is no closed form of above equation, ssCPsurvPH utilizes the uniroot function for numerical solution for n_0. Then $n = n_0 + n_1$, where both of n_0 and n_1 should be integers and hence n_0.

The consistency probability via Japan's criterion I (conditional version) under random effects model, $\Pr\left(\widetilde{D}_r \geq \pi \widetilde{D} | T > z_{1-\alpha}\right)$, is approximately

$$\frac{1}{1-\beta} \int_{u > z_\beta} \Phi\left(\frac{(1-\pi)(u + z_{1-\alpha} + z_{1-\beta})}{\sqrt{\rho_r^{-1} - 1}}\right) d\Phi(u)$$

where $\rho_r^{-1} - 1 = \frac{h_r}{h_r+1} \sum_{j \neq r}^{R} \frac{h_j}{h_j+1}, w = \frac{1}{\tau^2} \sum_{j=1}^{R} \frac{h_j}{h_j+1}, h_r = \tau^2/\sigma^{2(r)}, \sigma^{2(r)} = \Omega_r/(n_0 f_r)$. Since there is no closed form of above equation, ssCPsurvPH utilizes the integrate function for numerical integration.

Note for survival endpoint under PH assumption, $\Omega_r = (\ell + 1)^2/\{\ell(P_0^{(r)} + \ell P_1^{(r)})\}, P_k^{(r)} = 1 - e^{-\lambda_k^{(r)} L}$. δ and τ are derived based on the naive approach as the mean and standard deviation of the regional hazard ratios.

Value

A list containing the following components:

`n0` The overall sample size of the control group

`n1` The overall sample size of the treatment group

`n` The overall sample size.

`CP` The consistency probability, a scalar.

`"error: condition not met. negative n0 returned"`

`"error: regional fractions do not sum up to 1"` When vector f does not sum up to 1

Examples

```
ssCPsurvPH(alpha=0.025, beta=0.2, lambda0r=rep(0.05,3), hr=c(0.7,0.6,0.4), pi=0.5, randRatio=1, target=1, f=r
```

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