

Package ‘ssMRCT’

July 20, 2025

Type Package

Title Regional consistency evaluation and sample size calculation for MRCT

Version 0.1.0

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Description A comprehensive suite of functions for designing and analyzing Multi-Regional Clinical Trials (MRCTs), featuring specialized 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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Encoding UTF-8

LazyData true

NeedsCompilation no

Roxygen list(markdown = TRUE)

RoxygenNote 7.3.2

Depends R (>= 3.5.0)

Imports cubature, stats

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ssMRCT-package	<i>Regional consistency evaluation and sample size calculation for MRCTs</i>
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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.

Kunhai Qing, Xinru Ren, Shuping Jiang, Ping Yang, Menggang Yu and Jin Xu (2025). Regional consistency evaluation and sample size calculation under two MRCTs.

conProb	<i>Consistency probability for one MRCT via Japan's criterion I (conditional version)</i>
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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), $\Pr(D_k \geq \pi D \mid T > z_{1-\alpha})$, 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,

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

Then $N = N^{(t)} + N^{(c)}$. Additionally, both of $N^{(t)}$ and $N^{(c)}$ 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), $\Pr(D_{k,\text{pool}} \geq \pi D_{\text{pool}} \mid T^{(1)} > z_{1-\alpha}, T^{(2)} > z_{1-\alpha})$, is approximately

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

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

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

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., $\sigma^{2(t,1)} = \sigma^{2(t,2)}, \sigma^{2(c,1)} = \sigma^{2(c,2)}, d^{(1)} = d^{(2)}$ and $r^{(1)} = r^{(2)}$, then the above equation reduces to

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

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](#). But additionally requiring all of $N_k^{(t)}$ and $N_k^{(c)}$ should be integers and hence $N^{(t)}$, $N^{(c)}$ and N .

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	<i>Consistency probability for one MRCT via Japan's criterion II (conditional version)</i>
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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 $K \times 1$ 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),

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

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](#).

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	<i>Consistency probability for two MRCTs via Japan's criterion II (conditional version)</i>
------------	---

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 $K \times 1$ 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 $K \times 1$ 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),

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

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](#).

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")

```

regFrac	<i>Regional fraction for one MRCT via Japan's criterion I (conditional version)</i>
---------	---

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:

$$\text{conProb}(rF) - CP = 0$$

where $rF \in (0, 1)$.

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	<i>Regional fraction for two MRCTs via the extended Japan's criterion I (conditional version)</i>
----------	---

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:

$$\text{conProb2}(\text{rF2} \cdot k, \text{rF2}) - \text{CP} = 0$$

where $\text{rF2} \in (0, \min(1/k, 1))$,

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)
```

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