Package 'ThreeArmedTrials'

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Type Package

Title Design and Analysis of Clinical Non-Inferiority or Superiority Trials with Active and Placebo Control

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Description Design and analyze three-arm non-inferiority or superiority trials which follow a gold-standard design, i.e. trials with an experimental treatment, an active, and a placebo control. Method for the following distributions are implemented: Poisson (Mielke and Munk (2009) <arXiv:0912.4169>), negative binomial (Muetze et al. (2016) <doi:10.1002/sim.6738>), normal (Pigeot et al. (2003) <doi:10.1002/sim.1450>; Hasler et al. (2009) <doi:10.1002/sim.3052>), binary (Friede and Kieser (2007) <doi:10.1002/sim.2543>), nonparametric (Muetze et al. (2017) <doi:10.1002/sim.7176>), exponential (Mielke and Munk (2009) <arXiv:0912.4169>).

Depends R (>= 3.0.0)

Imports stats, MASS, methods, numDeriv

Suggests testthat, knitr, rmarkdown

License GPL (>= 3)

NeedsCompilation yes

URL https://github.com/tobiasmuetze/ThreeArmedTrials

BugReports https://github.com/tobiasmuetze/ThreeArmedTrials/issues

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R topics documented:

`check_missing` *check_missing*

Description

Check if all arguments are defined

Usage

```
check_missing(args = NULL, envir = parent.frame())
```

Arguments

`args`	Character vector of arguments to be checked for existence.
`envir`	Environment in which the arguments are defined.

`check_RET_arguments` *check_RET_arguments*

Description

Check arguments for their respective condition

Usage

```
check_RET_arguments(sig.level, power, Delta, n, allocation)
```

Arguments

sig.level	A numeric value specifying the significance level (type I error probability)
power	A numeric value specifying the target power (1 - type II error probability)
Delta	A numeric value specifying the non-inferiority or superiority margin. Is between 0 and 1 in case of non-inferiority and larger than 1 in case of superiority.
n	The total sample size. Needs to be at least 7.
allocation	A (non-empty) vector specifying the sample size allocation (nExp/n, nRef/n, nPla/n)

GElesions *Total number of new galodinium-enhancing lesions.*

Description

A (fictional) dataset containing the total number of new galodinium-enhancing lesions for different treatments for multiple sclerosis.

Usage

```
GElesions
```

Format

A data frame with 50 rows and 3 variables:

placebo Placebo group

reference Reference group

experimental Experimental treatment group

---

is.naturalnumber *is.naturalnumber*

Description

check if input is natural number

Usage

```
is.naturalnumber(x, tol = .Machine$double.eps^0.5)
```

Arguments

x	numeric number to be checked
tol	maximum accepted tolerance when checking if natural

loglikelihood_binary *loglikelihood_binary*

Description

log likelihood of Bernoulli function

Usage

```
loglikelihood_binary(p, xExp, xRef, xPla)
```

Arguments

p	numeric vector of probabilities with length 3
xExp	numeric vector of probabilities with length 3
xRef	numeric vector of probabilities with length 3
xPla	numeric vector of probabilities with length 3

opt_alloc_RET *Optimal sample size for three-arm trials when analyzed with a Wald-type test*

Description

Calculate optimal sample size allocation for Wald-type test for superiority or non-inferiority of the experimental treatment versus reference treatment with respect to placebo

Usage

```
opt_alloc_RET(experiment, reference, placebo, Delta, distribution, h = NULL)
```

Arguments

experiment	a numeric vector specifying the parameters of the experimental treatment group in the alternative hypothesis
reference	a numeric vector specifying the parameters of the reference treatment group in the alternative hypothesis
placebo	a numeric vector specifying the parameters of the placebo treatment group in the alternative hypothesis
Delta	a numeric value specifying the non-inferiority/superiority margin
distribution	a character specifying the distribution of the endpoints. Must must be either of "poisson", "negbin", "exponential", "normal"
h	Function measuring the efficacy; used to defined hypothesis

Details

The arguments `experiment`, `reference`, and `placebo` define the parameters of the endpoint distribution for the respective groups:
`distribution = "poisson"`: `experiment`, `reference`, and `placebo` must have length one and define the means.
`distribution = "negbin"`: `experiment`, `reference`, and `placebo` must have length two and define the mean in the first entry and the shape parameter in the second entry.
`distribution = "exponential"`: `experiment`, `reference`, and `placebo` must have length two and define the mean in the first entry and the probability for an uncensored observation in the second entry.
`distribution = "normal"`: `experiment`, `reference`, and `placebo` must have length two and define the mean in the first entry and the variance in the second entry.

Value

Vector with optimal sample size allocation in the order (experiment, reference, placebo)

Examples

```
opt_alloc_RET(experiment = 1,
              reference = 1,
              placebo = 3,
              Delta = 0.8,
              distribution = "poisson")
```

---

power_RET *Power related calculations for three-arm clinical trials*

Description

Compute power, sample size, or level of significance for Wald-type test for non-inferiority or superiority of the experimental treatment versus reference treatment with respect to placebo.

Usage

```
power_RET(
  experiment,
  reference,
  placebo,
  Delta,
  sig_level = NULL,
  power = NULL,
  n = NULL,
  allocation = c(1/3, 1/3, 1/3),
  distribution = NULL,
  ...
)
```

Arguments

experiment	a numeric vector specifying the parameters of the experimental treatment group in the alternative hypothesis
reference	a numeric vector specifying the parameters of the reference treatment group in the alternative hypothesis
placebo	a numeric vector specifying the parameters of the placebo treatment group in the alternative hypothesis
Delta	a numeric value specifying the non-inferiority/superiority margin
sig_level	A numeric value specifying the significance level (type I error probability)
power	A numeric value specifying the target power (1 - type II error probability)
n	The total sample size. Needs to be at least 7.
allocation	A (non-empty) vector specifying the sample size allocation (nExp/n, nRef/n, nPla/n)
distribution	A character specifying the distribution of the endpoints. Must must be either of "binary", "poisson", "negbin", "exponential", "normal"
...	Further arguments. See details.

Details

If the individual group sample sizes, i.e. n*allocation are not natural number, the parameters *n* and *allocation* will be re-calculated.

The additional parameter var_estimation is a character string specifying how the variance for the Wald-type test statistic is estimated in the Poisson and negative binomial model. Must be *RML* for restricted maximum-likelihood, or *ML* for unrestricted maximum-likelihood

Value

A list with class "power.htest" containing the following components:

n	The total sample size
power	A numeric value specifying the target power
Delta	A numeric value specifying the non-inferiority or superiority margin.
sig.level	A character string specifying the significance level
type	A character string indicating what type of Wald-type test will be performed
allocation	A vector with the sample size allocation (nExp/n, nRef/n, nPla/n)
sig.level	The significance level (Type I error probability)
nExp	A numeric value specifying the number of sample in the experimental treatment group
nRef	A numeric value specifying the number of sample in the reference treatment group
nPla	A numeric value specifying the number of sample in the placebo treatment group

Examples

```
power_RET(experiment = 15, reference = 17, placebo = 20,
         Delta = 0.8, sig_level = 0.025, power = 0.8,
         allocation = c(1, 1, 1) / 3,
         var_estimation = "RML",
         distribution = "poisson")
```

---

remission *Remission in clinical trial in patients with depression.*

Description

A dataset indicating whether a patient went into remission defined as a HAM-D total score of <= 7.

Usage

```
remission
```

Format

A data frame with 88 rows and 3 variables:

placebo Placebo group

reference Reference group

experimental Experimental treatment group

---

seizures *Number of seizures per patient.*

Description

A (fictional) dataset containing the number of seizures per patient for different add-on treatments evaluating an anti-epileptic drug.

Usage

```
seizures
```

Format

A data frame with 18 rows and 3 variables:

pla Placebo group

ref Reference group

exp Experimental treatment group

T2lesions *Number of new and enlarging T2 lesions per patient.*

Description

A (fictional) dataset containing the number of new and enlarging T2 lesions per patient for different treatments for multiple sclerosis.

Usage

```
T2lesions
```

Format

A data frame with 150 rows and 3 variables:

pla Placebo group

ref Reference group

exp Experimental treatment group

test_RET *Wald-type test for three-arm trials*

Description

Wald-type test for superiority/non-inferiority of the experimental treatment versus reference treatment with respect to placebo.

Usage

```
test_RET(xExp, xRef, xPla, Delta, ...)
```

Arguments

xExp	A (non-empty) numeric vector of data values from the experimental treatment group.
xRef	A (non-empty) numeric vector of data values from the reference treatment group.
xPla	A (non-empty) numeric vector of data values from the placebo group.
Delta	A numeric value specifying the non-inferiority or superiority margin. Is between 0 and 1 in case of non-inferiority and larger than 1 in case of superiority.
...	Other named arguments such as distribution, var_estimation. See details for more information.

Details

Additional parameters include `distribution` and `var_estimation`.
The parameter `distribution` is a character string and indicates whether a parametric model should be used. If not specified retention of effect hypothesis is tested using sample means and variances. The following options exist: `"poisson"` (Poisson distribution), `"negbin"` (negative binomial distribution), `"normal"` (normal distribution), `"exponential"` (censored exponential). `"nonparametric"` (non-parametric). If the parameter `distribution` is not specified the effect and the variance for the test statistic are estimated by the sample means and sample variances.
The parameter `var_estimation` defines how the variance is estimated in the parametric models `"poisson"` and `"negbin"`. The following options exist: `RML` for the restricted maximum-likelihood estimator and `ML` (default) for the unrestricted maximum-likelihood estimator.

Value

A list with class "htest" containing the following components:

`statistic`	The value of the Wald-type test statistic.
`p.value`	The p-value for the Wald-type test.
`method`	A character string indicating what type of Wald-type-test was performed.
`estimate`	The estimated rates for each of the group as well as the maximum-likelihood estimator for the shape parameter.
`sample.size`	The total number of data points used for the Wald-type test.

References

I. Pigeot, J. Schaefer, J. Roehmel, D. Hauschke. (2008). *Assessing non-inferiority of a new treatment in a three-arm clinical trial including a placebo.* Statistics in Medicine. 30(6):883-99.

M. Hasler, R. Vonk, and LA. Hothorn. (2008). *Assessing non-inferiority of a new treatment in a three-arm trial in the presence of heteroscedasticity.* Statistics in Medicine, 27(4):490-503.

M. Mielke and A. Munk. (2009). *The assessment and planning of non-inferiority trials for retention of effect hypotheses-towards a general approach.* arXiv preprint arXiv:0912.4169.

T. Muetze, A. Munk, and T. Friede. (2016). *Design and analysis of three-arm trials with negative binomially distributed endpoints.* Statistics in Medicine, 35(4):505-521.

See Also

`power_RET`

Examples

```
# Negative binomially distributed endpoints
# Test for non-inferiority test. lambda_P=8, lambda_R = 4, lambda_E = 5, and phi = 1
# Delta = (lambda_P-lambda_E)/(lambda_P-lambda_R)
xExp <- rnbinom(60, mu = 5, size = 1)
xRef <- rnbinom(40, mu = 4, size = 1)
xPla <- rnbinom(40, mu = 8, size = 1)
Delta <- (8-5) / (8-4)
test_RET(xExp, xRef, xPla, Delta, var_estimation = 'RML', distribution = "negbin")
```

```
test_RET(xExp, xRef, xPla, Delta, var_estimation = 'ML', distribution = "negbin")

# Poisson distributed endpoints
# Test for non-inferiority test. lambda_P=8, lambda_R = 4, lambda_E = 5
# Delta = (lambda_P-lambda_E)/(lambda_P-lambda_R)
xExp <- rpois(60, lambda = 5)
xRef <- rpois(40, lambda = 4)
xPla <- rpois(40, lambda = 8)
Delta <- (8-5) / (8-4)
test_RET(xExp, xRef, xPla, Delta, var_estimation = 'RML', distribution = "poisson")
test_RET(xExp, xRef, xPla, Delta, var_estimation = 'ML', distribution = "poisson")

# Censored exponential distributed endpoints
# Test for non-inferiority test. lambda_P=3, lambda_R = 1, lambda_E = 2
# Probability for uncensored observation: 0.9
# Delta = (lambda_P-lambda_E)/(lambda_P-lambda_R)
x_exp <- matrix(c(rexp(40, rate = 1/2), rbinom(40, size = 1, prob = 0.9)),
                ncol = 2, byrow = FALSE)
x_ref <- matrix(c(rexp(40, rate = 1/1), rbinom(40, size = 1, prob = 0.9)),
                ncol = 2, byrow = FALSE)
x_pla <- matrix(c(rexp(40, rate = 1/3), rbinom(40, size = 1, prob = 0.9)),
                ncol = 2, byrow = FALSE)
Delta <- log(2/3) / log(1/3)
test_RET(xExp = x_exp,
                xRef = x_ref,
                xPla = x_pla,
                Delta = Delta,
                distribution = "exponential")
```

`ThreeArmedTrials` *Design and Analysis of Three-armed Clinical Non-Inferiority or Superiority Trials with Active and Placebo Control*

Description

The package **ThreeArmedTrials** provides functions for designing and analyzing non-inferiority or superiority trials with an active and a placebo control. Non-inferiority and superiority are defined through the hypothesis $(\lambda_P-\lambda_E)/(\lambda_P-\lambda_R) \leq \Delta$ with the alternative hypothesis $(\lambda_P-\lambda_E)/(\lambda_P-\lambda_R) > \Delta$. The parameters λ_E, λ_R, and λ_P are associated with the distribution of the endpoints and smaller values of λ_E, λ_R, and λ_P are considered to be desirable. A detailed description of these parameters can be found in the help file of the individual functions. The margin Δ is between 0 and 1 for testing non-inferiority and larger than 1 for testing superiority.

A detailed discussion of the hypothesis can be found in Hauschke and Pigeot (2005).

The statistical theory for negative binomial distributed endpoint has been developed by Muetze et al. (2015).

Author(s)

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References

Hauschke, D. and Pigeot, I. 2005. "Establishing efficacy of a new experimental treatment in the 'gold standard' design." Biometrical Journal 47, 782–786. Muetze, T. et al. 2015. "Design and analysis of three-arm trials with negative binomially distributed endpoints." *Submitted.*

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