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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| check_missing | check_missing |

Description

Check if all arguments are defined

Usage

```r
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.

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| check_RET_arguments | check_RET_arguments |

Description

Check arguments for their respective condition

Usage

```r
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

Description

log likelihood of Bernoulli function

Usage

loglikelihood_binary(p, xExp, xRef, xPla)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>numeric vector of probabilities with length 3</td>
</tr>
<tr>
<td>xExp</td>
<td>numeric vector of probabilities with length 3</td>
</tr>
<tr>
<td>xRef</td>
<td>numeric vector of probabilities with length 3</td>
</tr>
<tr>
<td>xPla</td>
<td>numeric vector of probabilities with length 3</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>experiment</td>
<td>a numeric vector specifying the parameters of the experimental treatment group in the alternative hypothesis</td>
</tr>
<tr>
<td>reference</td>
<td>a numeric vector specifying the parameters of the reference treatment group in the alternative hypothesis</td>
</tr>
<tr>
<td>placebo</td>
<td>a numeric vector specifying the parameters of the placebo treatment group in the alternative hypothesis</td>
</tr>
<tr>
<td>Delta</td>
<td>a numeric value specifying the non-inferiority/superiority margin</td>
</tr>
<tr>
<td>distribution</td>
<td>a character specifying the distribution of the endpoints. Must must be either of &quot;poisson&quot;, &quot;negbin&quot;, &quot;exponential&quot;, &quot;normal&quot;</td>
</tr>
<tr>
<td>h</td>
<td>Function measuring the efficacy; used to defined hypothesis</td>
</tr>
</tbody>
</table>
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

```r
opt_alloc_RET(experiment = 1L,
             reference = 1L,
             placebo = 3L,
             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

```r
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 be either of "binary", "poisson", "negbin", "exponential", "normal"

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 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 \( \leq 7 \).

Usage
remission

Format
A data frame with 88 rows and 3 variables:

- **placebo**: Placebo group
- **reference**: Reference group
- **experimental**: Experimental treatment group

---

seizures

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

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")
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 \(\lambda_E, \lambda_R, \text{ and } \lambda_P\) are associated with the distribution of the endpoints and smaller values of \(\lambda_E, \lambda_R, \text{ and } \lambda_P\) are considered to be desirable. A detailed description of these parameters can be found in the help file of the individual functions. The margin \(\Delta\) 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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