Package ‘ThreeArmedTrials’

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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-armed non-inferiority or superiority trials which follow a gold-standard design, i.e. trials with an experimental treatment, an active and a placebo control. The following distribution of endpoints is covered: negative binomial distribution.

Depends R (>= 3.0.0)

Imports stats, MASS

License GPL (>= 2)

NeedsCompilation yes

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ThreeArmedTrials-package

*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 \( \frac{\lambda_P - \lambda_E}{\lambda_P - \lambda_R} \leq \Delta \) with the alternative hypothesis \( \frac{\lambda_P - \lambda_E}{\lambda_P - \lambda_R} > \Delta \). The parameters \( \lambda_E, \lambda_R, \) and \( \lambda_P \) are associated with the distribution of the endpoints and smaller values of \( \lambda_E, \lambda_R, \) 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).

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**References**


**power.taNegbin.test**

*Power related calcuations for three-armed clinical trials with negative binomial distributed endpoints*

**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.taNegbin.test(rateExp, rateRef, ratePla, shape, Delta, sig.level = NULL,
                   power = NULL, n = NULL, type = c("restricted", "unrestricted"),
                   allocation = c(1/3, 1/3, 1/3))
```

Arguments

- `rateExp`: A numeric value specifying the rate of the experimental treatment group in the alternative hypothesis.
- `rateRef`: A numeric value specifying the rate of the reference treatment group in the alternative hypothesis.
- `ratePla`: A numeric value specifying the rate of the placebo treatment group in the alternative hypothesis.
- `shape`: A numeric value specifying the shape parameter.
- `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.
- `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.
- `type`: A character string determining how the variance for the Wald-type test statistic is estimated, must be `restricted`, or `unrestricted`.
- `allocation`: A (non-empty) vector specifying the sample size allocation (nExp/n, nRef/n, nPla/n).

Details

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

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

# Example for type = 'unrestricted': Calculation of n, power, and sig level.
# Expect n=1038, power=0.8, sig level=0.025, respectively
power.taNegbin.test(rateExp = 2, rateRef = 2, ratePla = 4, shape = 0.5, Delta = 0.8,
sig.level = 0.025, power = 0.8, type = 'unrestricted', allocation = c(1/3, 1/3, 1/3))

# Example for type = 'restricted' calculation of n, power, and sig level.
# Expect n=1092, power=0.8, sig level=0.025
power.taNegbin.test(rateExp = 2, rateRef = 2, ratePla = 4, shape = 0.5, Delta = 0.8,
sig.level = 0.025, power = 0.8, type = 'restricted', allocation = c(1/3, 1/3, 1/3))

# Example for recalculation of 'allocation' and 'n'
power.taNegbin.test(rateExp = 2, rateRef = 2, ratePla = 4, shape = 0.5, Delta = 0.8,
n = 1001, power = 0.8, allocation = c(0.25, 0.5, 0.25))
Delta  A numeric value specifying the non-inferiority/superiority margin

Type  A character string determining how the variance for the Wald-type test statistic is estimated, must be restricted, or unrestricted

n  The total sample size. This parameter is only mandatory for type='restricted'. For type='unrestricted', this parameter is optional.

sig.level  A numeric value specifying the significance level (type I error probability). This parameter is only mandatory for type='restricted'. For type='unrestricted', this parameter is optional.

Value

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

n  The total sample size. Not mandatory.

Delta  A numeric value specifying the non-inferiority/superiority margin

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)

rateExp  A numeric value specifying the rate of the experimental treatment group in the alternative hypothesis

rateRef  A numeric value specifying the rate of the reference treatment group in the alternative hypothesis

ratePla  A numeric value specifying the rate of the placebo treatment group in the alternative hypothesis

shape  A numeric value specifying the shape parameter

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

# Example for type = 'unrestricted'
tanegbinOptAllocation(rateExp = 2, rateRef = 2, ratePla = 4, shape = 0.5, Delta = 0.8, type = 'unrestricted', n = 1048, sig.level = 0.025)
tanegbinOptAllocation(rateExp = 2, rateRef = 2, ratePla = 4, shape = 0.5, Delta = 0.8, type = 'unrestricted')

# Example for type = 'restricted'.
## Not run:
tanegbinOptAllocation(rateExp = 2, rateRef = 2, ratePla = 4, shape = 0.5, Delta = 0.8, type = 'restricted', n = 500, sig.level = 0.025)

## End(Not run)
taNegbin.test  

Statistical test for three-armed clinical trials with negative binomial distributed endpoints.

Description

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

Usage

\[
\text{taNegbin.test(xExp, xRef, xPla, Delta, method = c("RML", "ML", 
"SampleVariance"))}
\]

Arguments

- **xExp**: A (non-empty) numeric vector of data values coming from the experimental treatment group.
- **xRef**: A (non-empty) numeric vector of data values coming from the reference treatment group.
- **xPla**: A (non-empty) numeric vector of data values coming 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.
- **method**: A character string determining how the variance for the Wald-type test statistic is estimated, must be RML, ML, or SampleVariance.

Details

The hypothesis \((\lambda_P - \lambda_E)/(\lambda_P - \lambda_R) \leq \Delta\) is tested against the alternative \((\lambda_P - \lambda_E)/(\lambda_P - \lambda_R) > \Delta\). \(\lambda_E, \lambda_R, \lambda_P\) are the rates of the experimental treatment (rateExp), the reference treatment (rateRef), and the placebo group (ratePla), respectively. The margin Delta, i.e. \(\Delta\) in the formulas above, is between 0 and 1 for testing non-inferiority and larger than 1 for testing superiority. The parametrisation of the underlying negative binomial distributions is chosen such that a negative binomial distribution of rate \(\lambda\) and shape parameter \(\phi\) has variance \(\lambda(1 + \phi\lambda)\). The shape parameter \(\phi\) is assumed to be the same among the groups.

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

Muetze T et al. 2015. Statistical inference for three-arm trials with negative binomially distributed endpoints. (Submitted.)

See Also

power.taNegbin.test

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 <- rbinom(60, mu=5, size=1)
xRef <- rbinom(40, mu=4, size=1)
xPla <- rbinom(40, mu=8, size=1)
Delta <- (8-5)/(8-4)
taNegbin.test(xExp, xRef, xPla, Delta, method = 'RML')
taNegbin.test(xExp, xRef, xPla, Delta, method = 'ML')
taNegbin.test(xExp, xRef, xPla, Delta, method = 'SampleVariance')

# Test for superiority test. lambda_P=8, lambda_R = 5, lambda_E = 4, and phi = 1
# Delta = (lambda_P-lambda_E)/(lambda_P-lambda_R)
xExp <- rbinom(60, mu=5, size=1)
xRef <- rbinom(40, mu=4, size=1)
xPla <- rbinom(40, mu=8, size=1)
Delta <- (8-5)/(8-4)
taNegbin.test(xExp, xRef, xPla, Delta, method = 'RML')
taNegbin.test(xExp, xRef, xPla, Delta, method = 'ML')
taNegbin.test(xExp, xRef, xPla, Delta, method = 'SampleVariance')
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