

Package ‘DropTheLosersUEL’

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Type Package

Title Implementation of unconditional exact likelihood (UEL) testing and inference procedure for drop-the-losers designs for binary endpoints in the rare disease setting

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Author Ina Jazic, Xiaoyan Liu, Glen Laird

Maintainer Ina Jazic <Ina_Jazic@vrtx.com>

Description The drop-the-losers design was proposed to establish efficacy for one of several treatment arms more efficiently than the traditional development paradigm of separate studies for treatment selection and confirmation. A pre-specified number of patients receive each treatment in Stage 1, at the end of which the experimental treatment exhibiting the most efficacy proceeds to Stage 2, after which a hypothesis test of efficacy is conducted incorporating data from both stages.

This package implements the unconditional exact likelihood (UEL) test and corresponding confidence intervals, suitable for uncontrolled drop-the-losers designs for binary endpoints. Such a design is likely to arise in a rare disease setting. This test is based on the distribution of the total number of responses for the selected treatment arm. Power calculations for the UEL test are also implemented. Testing, inference, and power calculations have also been implemented for a normal approximation to the UEL test. Additional functions to aid in design decisions for such drop-the-losers designs are also included.

Imports ggplot2

License GPL-3

Encoding UTF-8

LazyData true

RoxygenNote 7.1.0

R topics documented:

ci_ztau	2
crit_ztau	3
est_pitau	3
meanvar_ztau	4
plot_power_pselecttrt	5
pval_ztau	5
pwr_ztau	6
p_select_trt	7
p_ties	8

Index	9
--------------	----------

ci_ztau

*Confidence interval based on UEL test***Description**

The function for obtaining a confidence interval for π_τ , the response rate for the treatment selected at the end of Stage 1, based on the UEL test. The observed response rates in the non-selected arms are used as plug-in estimates of the response rates in the non-selected arms. This function also supports confidence intervals for a normal approximation to the UEL test.

Usage

```
ci_ztau(
  resp.vec,
  tau,
  n1,
  n2,
  two.sided = TRUE,
  alpha = 0.05,
  precision = 1e-04,
  norm.approx = FALSE
)
```

Arguments

resp.vec	Vector of the observed number of responses for all treatment arms. Element τ of this vector contains responses from both stages
tau	Index for the selected treatment arm
n1	Number of subjects per treatment in Stage 1
n2	Number of subjects receiving the selected treatment τ in Stage 2
two.sided	Indicator of whether a two-sided confidence interval should be constructed; defaults to TRUE. If FALSE, the upper bound for the confidence interval will be 1
alpha	Specified such that a $(1-\alpha)$ confidence interval is constructed; defaults to 0.05
precision	Search for confidence bound stops when $ \text{Rejection prb} - \alpha/2 < \text{precision}$ if two.sided=TRUE (replace $\alpha/2$ with α if two.sided=FALSE); defaults to $1e-4$
norm.approx	Indicator of whether the normal approximation (with continuity correction) should be used instead of the UEL method; defaults to FALSE

Value

ci_ztau returns a vector with two elements: the lower and upper bound of the confidence interval.

Examples

```
ci_ztau(resp.vec=c(12,3,3), tau=1, n1=12, n2=12)
ci_ztau(resp.vec=c(24,10,10), tau=1, n1=40, n2=40, norm.approx=TRUE)
```

crit_ztau	<i>Critical value for UEL test</i>
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Description

The function for obtaining the critical value for a one-sided level α UEL test of π_τ vs. the specified π_0 , based on the distribution of Z_τ , the total number of responses (across Stages 1 and 2) for the treatment selected at the end of Stage 1. Such a test would be rejected if the observed Z_τ is greater than or equal to this critical value. This function also supports a normal approximation to the UEL test.

Usage

```
crit_ztau(pi0, ntrts, n1, n2, alpha = 0.025, norm.approx = FALSE)
```

Arguments

pi0	(Known) control or comparison response rate
ntrts	Number of treatments investigated in Stage 1
n1	Number of subjects per treatment in Stage 1
n2	Number of subjects receiving the selected treatment τ in Stage 2
alpha	Significance level; defaults to 0.025
norm.approx	Indicator of whether the normal approximation (with continuity correction) should be used instead of the UEL method; defaults to FALSE

Value

crit_ztau returns a single element with the critical value for a one-sided level-alpha test of π_τ vs. the specified π_0 .

Examples

```
crit_ztau(pi0=0.1, ntrts=3, n1 = 12, n2 = 12)
crit_ztau(pi0=0.1, ntrts=3, n1 = 40, n2 = 40, norm.approx=TRUE)
crit_ztau(pi0=0.1, ntrts=3, n1 = 40, n2 = 40, norm.approx=FALSE)
```

est_pitau	<i>Point estimator (UMVUE) for response rate for selected arm</i>
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Description

The function for an unbiased estimator of π_τ , the response rate for the treatment selected at the end of Stage 1. This is an implementation of the UMVUE originally proposed in Tappin (1992). This estimator will only be the UMVUE if the standard rules for selecting the τ are followed (i.e., the arm with the highest Stage 1 response will be selected; in case of ties, the treatment with the smallest index will be selected).

Usage

```
est_pitau(stage1.resp.vec, stage2.resp, tau, n1, n2)
```

Arguments

stage1.resp.vec	Vector of the observed number of responses for all treatment arms in Stage 1
stage2.resp	Observed number of responses for the selected treatment arm in Stage 2
tau	Index for the selected treatment arm
n1	Number of subjects per treatment in Stage 1
n2	Number of subjects receiving the selected treatment τ in Stage 2

Value

est_pitau returns a single element: the point estimate of the response rate π_τ .

Examples

```
est_pitau(stage1.resp.vec=c(5,3,3), stage2.resp=5, tau=1, n1=12, n2=12)
```

meanvar_ztau	<i>Mean and variance of Z_τ</i>
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Description

The function for obtaining the mean and variance of Z_τ , the total number of responses (across Stages 1 and 2) for the treatment selected at the end of Stage 1, for a specified vector of true response rates.

Usage

```
meanvar_ztau(pi, n1, n2)
```

Arguments

pi	Vector of response rates for each treatment
n1	Number of subjects per treatment in Stage 1
n2	Number of subjects receiving the selected treatment τ in Stage 2

Value

meanvar_ztau returns a list where the first element is the mean and the second element is the variance.

Examples

```
meanvar_ztau(pi = c(0.3, 0.3, 0.4), n1 = 11, n2 = 12)
```

plot_power_pselecttrt *Plot comparing overall study power and selection of a particular treatment at the end of Stage 1, for a fixed total sample size*

Description

The function for a plot that can help decide how a certain total sample size should be allocated between Stage 1 and Stage 2, for a specified vector of true response rates. For various combinations of Stage 1 and Stage 2 sample sizes (under the constraint of the total sample size), the overall study power and the probability of the specified treatment being selected at the end of Stage 1 are plotted as separate curves.

Usage

```
plot_power_pselecttrt(pi0, pi, tau, totalN, n1start = 5)
```

Arguments

pi0	(Known) control or comparison response rate
pi	Vector of response rates for each treatment
tau	Index for the treatment arm of interest
totalN	Total number of subjects in the study. In the plot, n1 and n2 are constrained to equal totalN, which is $n1 \times ntrts + n2$.
n1start	Minimum number of subjects per treatment in Stage 1; defaults to 5

Value

plot_power_pselecttrt returns a plot with two curves: the solid line represents the overall study power, and the dotted line represents the probability that treatment tau is selected.

Examples

```
plot_power_pselecttrt(pi0 = 0.1, pi = c(0.2, 0.2, 0.3), tau=1, totalN=45)
```

pval_ztau	<i>p-value for UEL test</i>
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Description

This function provides the p-value for for a one-sided level α UEL test of π_τ vs. the specified π_0 , based on the distribution of Z_τ , the total number of responses (across Stages 1 and 2) for the treatment selected at the end of Stage 1. This function also supports a normal approximation to the UEL test.

Usage

```
pval_ztau(z, pi0, ntrts, n1, n2, norm.approx = FALSE)
```

Arguments

<code>z</code>	Total (observed) number of responses (across Stages 1 and 2) for selected treatment τ
<code>pi0</code>	(Known) control or comparison response rate
<code>ntrts</code>	Number of treatments investigated in Stage 1
<code>n1</code>	Number of subjects per treatment in Stage 1
<code>n2</code>	Number of subjects receiving the selected treatment τ in Stage 2
<code>norm.approx</code>	Indicator of whether the normal approximation (with continuity correction) should be used instead of the UEL method, defaults to FALSE

Value

`pval_ztau` returns a single element with the p-value for a one-sided test of π_τ vs. the specified π_0 .

Examples

```
pval_ztau(z = 6, ntrts=3, pi0=0.1, n1 = 12, n2 = 12)
pval_ztau(z = 6, ntrts=3, pi0=0.1, n1 = 40, n2 = 40, norm.approx=TRUE)
pval_ztau(z = 6, ntrts=3, pi0=0.1, n1 = 40, n2 = 40, norm.approx=FALSE)
```

`pwr_ztau`

Power and type 1 error for UEL test

Description

The function for obtaining power/type 1 error for a one-sided level alpha UEL test of π_τ vs. the specified π_0 , based on the distribution of Z_τ , the total number of responses (across Stages 1 and 2) for the treatment selected at the end of Stage 1. This function also supports a normal approximation to the UEL test.

Usage

```
pwr_ztau(pi0, ntrts, pi.alt = NA, n1, n2, alpha = 0.025, norm.approx = FALSE)
```

Arguments

<code>pi0</code>	(Known) control or comparison response rate
<code>ntrts</code>	Number of treatments investigated in Stage 1
<code>pi.alt</code>	Vector of response rates under the alternative hypothesis with length <code>ntrts</code>
<code>n1</code>	Number of subjects per treatment in Stage 1
<code>n2</code>	Number of subjects receiving the selected treatment τ in Stage 2
<code>alpha</code>	Significance level; defaults to 0.025
<code>norm.approx</code>	Indicator of whether the normal approximation (with continuity correction) should be used instead of the UEL method; defaults to FALSE

Value

If `pi.alt` is not provided, then `pwr_ztau` returns a list containing the critical value and the type 1 error. If `pi.alt` is provided, then `pwr_ztau` returns a list containing the critical value and power. For `norm.approx=FALSE`, type 1 error/power by treatment is also provided as a third element in the list.

Examples

```
pwr_ztau(pi0=0.1, ntrts=3, pi.alt = c(0.3, 0.1, 0.1), n1 = 12, n2 = 12)
pwr_ztau(pi0=0.1, ntrts=3, n1=12, n2=12)
```

p_select_trt	<i>Probability of selecting a particular treatment at the end of Stage 1</i>
--------------	--

Description

The function for obtaining the probability that a given treatment is selected at the end of Stage 1 to proceed to Stage 2, for a specified vector of true response rates. A tie-breaking rule applies such that ties are broken in favor of the treatment with a lower index (e.g., 1 over 2). In other words, this function computes the probability that a given treatment has the highest observed number of responses in Stage 1, either outright or if it is favored in a tie.

Usage

```
p_select_trt(tau, pi, n1)
```

Arguments

tau	Index for the treatment arm of interest
pi	Vector of response rates for each treatment
n1	Number of subjects per treatment in Stage 1

Value

`p_select_trt` returns the numeric probability that treatment `tau` is selected.

Examples

```
p_select_trt(tau = 1, pi = c(0.3, 0.2, 0.2), n1 = 12)
```

<code>p_ties</code>	<i>Probability of ties in the highest number of observed responses in Stage 1</i>
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Description

The function for calculating the probability of ties in the highest number of observed responses in Stage 1, for a specified vector of true response rates.

Usage

```
p_ties(pi, n1)
```

Arguments

<code>pi</code>	Vector of response rates for each treatment
<code>n1</code>	Number of subjects per treatment in Stage 1

Value

`plot_power_pselecttrt` returns a vector of length k , where k is the number of treatments (length `pi`), indicating the probabilities of 2-group ties through $(k-1)$ -group ties, as well as the total probability of ties.

Examples

```
p_ties(pi = c(0.2, 0.2, 0.3), n1=12)
```


Index

ci_ztau, [2](#)
crit_ztau, [3](#)

est_pitau, [3](#)

meanvar_ztau, [4](#)

p_select_trt, [7](#)
p_ties, [8](#)
plot_power_pselecttrt, [5](#)
pval_ztau, [5](#)
pwr_ztau, [6](#)