Package ‘gscounts’

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Type Package

Title Group Sequential Designs with Negative Binomial Outcomes

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Description Design and analysis of group sequential designs for negative binomial outcomes, as described by T Mütze, E Glimm, H Schmidli, T Friede (2018) <doi:10.1177/0962280218773115>.

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License GPL (>= 2)

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

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`design_gsnb` *Group sequential design with negative binomial outcomes*

Description

Design a group sequential trial with negative binomial outcomes

Usage

```
design_gsnb(
  rate1,
  rate2,
  dispersion,
  ratio_H0 = 1,
  random_ratio = 1,
  power,
  sig_level,
  timing,
  esf = obrien,
  esf_futility = NULL,
  futility = NULL,
  t_recruit1 = NULL,
  t_recruit2 = NULL,
  study_period = NULL,
  accrual_period = NULL,
  followup_max = NULL,
  accrual_speed = 1,
  ...
)
```

Arguments

`rate1`	numeric; assumed rate of treatment group 1 in the alternative
`rate2`	numeric; assumed rate of treatment group 2 in the alternative
`dispersion`	numeric; dispersion (shape) parameter of negative binomial distribution
`ratio_H0`	numeric; positive number denoting the rate ratio μ_1/μ_2 under the null hypothesis, i.e. the non-inferiority or superiority margin
`random_ratio`	numeric; randomization ratio n1/n2

power	numeric; target power of group sequential design
sig_level	numeric; Type I error / significance level
timing	numeric vector; 0 < timing[1] < ... < timing[K] = 1 with K the number of analyses, i.e. (K-1) interim analyses and final analysis. When the timing of efficacy and futility analyses differ, timing should not be defined. Instead, the arguments timing_eff and timing_fut have to be used to specify the timing of the efficacy and futility analyses, respectively.
esf	function; error spending function
esf_futility	function; futility error spending function
futility	character; either "binding", "nonbinding", or NULL for binding, nonbinding, or no futility boundaries
t_recruit1	numeric vector; recruit (i.e. study entry) times in group 1
t_recruit2	numeric vector; recruit (i.e. study entry) times in group 2
study_period	numeric; study duration; to be set when follow-up times are not identical between subjects, NULL otherwise
accrual_period	numeric; accrual period
followup_max	numeric; maximum exposure time of a subject; to be set when follow-up times are to be equal for each subject, NULL otherwise
accrual_speed	numeric; determines accrual speed; values larger than 1 result in accrual slower than linear; values between 0 and 1 result in accrual faster than linear.
...	further arguments. Will be passed to the error spending function.

Details

Denote μ_1 and μ_2 the event rates in treatment groups 1 and 2. This function considers smaller event rates to be better. The statistical hypothesis testing problem of interest is

$$H_0 : \frac{\mu_1}{\mu_2} \geq \delta vs. H_1 : \frac{\mu_1}{\mu_2} < \delta,$$

with $\delta =$ratio_H0. Non-inferiority of treatment group 1 compared to treatment group 2 is tested for $\delta \in (1, \infty)$. Superiority of treatment group 1 over treatment group 2 is tested for $\delta \in (0, 1]$. The calculation of the efficacy and (non-)binding futility boundaries are performed under the hypothesis $H_0 : \frac{\mu_1}{\mu_2} = \delta$ and under the alternative $H_1 : \frac{\mu_1}{\mu_2} =$rate1 / rate2.

The argument ‘accrual_speed‘ is used to adjust the accrual speed. Number of subjects in the study at study time t is given by $f(t) = a * t^b$ with $a = n/accrual_period$ and $b = accrual_speed$ For linear recruitment, $b = 1$. $b > 1$ results is slower than linear recruitment for $t < accrual_period$ and faster than linear recruitment for $t > accrual_period$. Vice verse for $b < 1$.

Value

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

rate1	as input
rate2	as input

`dispersion`	as input
`power`	as input
`timing`	as input
`ratio_H0`	as input
`ratio_H1`	ratio `rate1/rate2`
`sig_level`	as input
`random_ratio`	as input
`power_fix`	power of fixed design
`expected_info`	list; expected information under `ratio_H0` and `ratio_H1`
`efficacy`	list; contains the elements `esf` (type I error spending function), `spend` (type I error spend at each look), and `critical` (critical value for efficacy testing)
`futility`	list; only part of the output if argument `futility` is defined in the input. Contains the elements `futility` (input argument `futility`), `esf` (type II error spending function), `spend` (type II error spend at each look), and `critical` (critical value for futility testing)
`stop_prob`	list; contains the element `efficacy` with the probabilities for stopping for efficacy and, if futility bounds are calculated, the element `futility` with the probabilities for stopping for futility
`t_recruit1`	as input
`t_recruit2`	as input
`study_period`	as input
`followup_max`	as input
`max_info`	maximum information
`calendar`	calendar times of data looks; only calculated when exposure times are not identical

References

Mütze, T., Glimm, E., Schmidli, H., & Friede, T. (2018). Group sequential designs for negative binomial outcomes. Statistical Methods in Medical Research, <doi:10.1177/0962280218773115>.

Examples

```
# Calculate the sample sizes for a given accrual period and study period (without futility)
out <- design_gsnb(rate1 = 0.0875, rate2 = 0.125, dispersion = 5,
                   power = 0.8, timing = c(0.5, 1), esf = obrien,
                   ratio_H0 = 1, sig_level = 0.025,
                   study_period = 3.5, accrual_period = 1.25, random_ratio = 1)
out

# Calculate the sample sizes for a given accrual period and study period with binding futility
out <- design_gsnb(rate1 = 0.0875, rate2 = 0.125, dispersion = 5,
                   power = 0.8, timing = c(0.5, 1), esf = obrien,
                   ratio_H0 = 1, sig_level = 0.025, study_period = 3.5,
                   accrual_period = 1.25, random_ratio = 1, futility = "binding",
```

```
                   esf_futility = obrien)
out


# Calculate study period for given recruitment times
expose <- seq(0, 1.25, length.out = 1042)
out <- design_gsnb(rate1 = 0.0875, rate2 = 0.125, dispersion = 5,
                   power = 0.8, timing = c(0.5, 1), esf = obrien,
                   ratio_H0 = 1, sig_level = 0.025, t_recruit1 = expose,
                   t_recruit2 = expose, random_ratio = 1)
out

# Calculate sample size for a fixed exposure time
out <- design_gsnb(rate1 = 0.0875, rate2 = 0.125, dispersion = 5,
                   power = 0.8, timing = c(0.5, 1), esf = obrien,
                   ratio_H0 = 1, sig_level = 0.025,
                   followup_max = 0.5, random_ratio = 1)

# Different timing for efficacy and futility analyses
 design_gsnb(rate1 = 1, rate2 = 2, dispersion = 5,
             power = 0.8, esf = obrien,
             ratio_H0 = 1, sig_level = 0.025, study_period = 3.5,
             accrual_period = 1.25, random_ratio = 1, futility = "binding",
             esf_futility = pocock,
             timing_eff = c(0.8, 1),
             timing_fut = c(0.2, 0.5, 1))
```

---

design_nb *Clinical trials with negative binomial outcomes*

Description

Design a clinical trial with negative binomial outcomes

Usage

```
design_nb(
  rate1,
  rate2,
  dispersion,
  power,
  ratio_H0 = 1,
  sig_level,
  random_ratio = 1,
  t_recruit1 = NULL,
  t_recruit2 = NULL,
  study_period = NULL,
  accrual_period = NULL,
  followup_max = NULL,
```

```
  accrual_speed = 1
)
```

Arguments

`rate1`	numeric; assumed rate of treatment group 1 in the alternative
`rate2`	numeric; assumed rate of treatment group 2 in the alternative
`dispersion`	numeric; dispersion (shape) parameter of negative binomial distribution
`power`	numeric; target power
`ratio_H0`	numeric; positive number denoting the rate ratio rate_1/rate_2 under the null hypothesis, i.e. the non-inferiority or superiority margin
`sig_level`	numeric; Type I error / significance level
`random_ratio`	numeric; randomization ratio n1/n2
`t_recruit1`	numeric vector; recruit (i.e. study entry) times in group 1
`t_recruit2`	numeric vector; recruit (i.e. study entry) times in group 2
`study_period`	numeric; study duration
`accrual_period`	numeric; accrual period
`followup_max`	numeric; maximum exposure time of a patient
`accrual_speed`	numeric; determines accrual speed; values larger than 1 result in accrual slower than linear; values between 0 and 1 result in accrual faster than linear.

Value

A list containing the following components:

`rate1`	as input
`rate2`	as input
`dispersion`	as input
`power`	as input
`ratio_H0`	as input
`ratio_H1`	ratio `rate1/rate2`
`sig_level`	as input
`random_ratio`	as input
`t_recruit1`	as input
`t_recruit2`	as input
`study_period`	as input
`followup_max`	as input
`max_info`	maximum information

Examples

```
# Calculate sample size for given accrual period and study duration assuming uniformal accrual
out <- design_nb(rate1 = 0.0875, rate2 = 0.125, dispersion = 5, power = 0.8,
                 ratio_H0 = 1, sig_level = 0.025,
                 study_period = 4, accrual_period = 1, random_ratio = 2)
out

# Calculate sample size for a fixed exposure time of 0.5 years
out <- design_nb(rate1 = 4.2, rate2 = 8.4, dispersion = 3, power = 0.8,
                 ratio_H0 = 1, sig_level = 0.025,
                 followup_max = 0.5, random_ratio = 2)
out

# Calculate study period for given recruitment time
t_recruit1 <- seq(0, 1.25, length.out = 1200)
t_recruit2 <- seq(0, 1.25, length.out = 800)
out <- design_nb(rate1 = 0.0875, rate2 = 0.125, dispersion = 5, power = 0.8,
                 ratio_H0 = 1, sig_level = 0.025,
                 t_recruit1 = t_recruit1, t_recruit2 = t_recruit2)
```

---

get_calendartime_gsnb *Calendar time of data looks*

Description

Calculate the calendar time of looks given the information time

Usage

```
get_calendartime_gsnb(
  rate1,
  rate2,
  dispersion,
  t_recruit1,
  t_recruit2,
  timing,
  followup1,
  followup2
)
```

Arguments

rate1	numeric; rate in treatment group 1
rate2	numeric; rate in treatment group 2
dispersion	numeric; dispersion (shape) parameter of negative binomial distribution
t_recruit1	numeric vector; recruit (i.e. study entry) times in group 1
t_recruit2	numeric vector; recruit (i.e. study entry) times in group 2

`timing`	numeric vector with entries in (0,1]; information times of data looks
`followup1`	numeric vector; final individual follow-up times in treatment group 1
`followup2`	numeric vector; final individual follow-up times in treatment group 2

Value

numeric; vector with calendar time of data looks

Examples

```
# Calendar time at which 50%, 75%, and 100% of the maximum information is attained
# 100 subjects in each group are recruited uniformly over 1.5 years
# Study ends after two years, i.e. follow-up times vary between 2 and 0.5 years
get_calendartime_gsnb(rate1 = 0.1,
                      rate2 = 0.125,
                      dispersion = 5,
                      t_recruit1 = seq(0, 1.5, length.out = 100),
                      t_recruit2 = seq(0, 1.5, length.out = 100),
                      timing = c(0.5, 0.75, 1),
                      followup1 = seq(2, 0.5, length.out = 100),
                      followup2 = seq(2, 0.5, length.out = 100))
```

get_info_gsnb *Information level for log rate ratio*

Description

Calculates the information level for the log rate ratio of the negative binomial model

Usage

```
get_info_gsnb(rate1, rate2, dispersion, followup1, followup2)
```

Arguments

`rate1`	numeric; rate in treatment group 1
`rate2`	numeric; rate in treatment group 2
`dispersion`	numeric; dispersion (shape) parameter of negative binomial distribution
`followup1`	numeric vector; individual follow-up times in treatment group 1
`followup2`	numeric vector; individual follow-up times in treatment group 2

Value

numeric; information level

Examples

```
# Calculates information level for case of 10 subjects per group
# Follow-up times of subjects in each group range from 1 to 3
get_info_gsnb(rate1 = 0.1,
              rate2 = 0.125,
              dispersion = 4,
              followup1 = seq(1, 3, length.out = 10),
              followup2 = seq(1, 3, length.out = 10))
```

gscounts *gscounts*

Description

Design and monitoring of group sequential designs with negative binomial data.

Author(s)

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hospitalizations *Hospitalizations*

Description

A dataset containing the hospitalization times of 1980 patients:

Usage

```
data(hospitalizations)
```

Format

A data frame with 2323 rows and 4 variables

Details

- treatment. Treatment identifier.
- pat. Patient identifier. Unique within `treatment`
- t_recruit. Recruitment time of patient into the clinical trial.
- eventtime. Event time of hospitalization. `NA` corresponds to no event.

obrien *obrien*

Description

Error spending function mimicking O'Brien & Fleming critical values

Usage

```
obrien(t, sig_level, ...)
```

Arguments

t	numeric; Non-negative information ratio
sig_level	numeric; significance level
...	optional arguments

Value

numeric

Examples

```
# O'Brien-Fleming-type error spending function
obrien(t = c(0.5, 1), sig_level = 0.025)
```

pocock *pocock*

Description

Error spending function mimicking Pococks critical values

Usage

```
pocock(t, sig_level, ...)
```

Arguments

t	numeric; Non-negative information ratio
sig_level	numeric; significance level
...	optional arguments

Value

numeric

Examples

```
# Pocock-type error spending function
pocock(t = c(0.5, 1), sig_level = 0.025)
```

`print.gsnb` *print.gsnb*

Description

print method for instance of class gsnb

Usage

```
## S3 method for class 'gsnb'
print(x, ...)
```

Arguments

`x`	an object of class gsnb
`...`	optional arguments to print or plot methods

`print.nb` *print.nb*

Description

print method for instance of class nb

Usage

```
## S3 method for class 'nb'
print(x, ...)
```

Arguments

`x`	an object of class nb
`...`	optional arguments to print or plot methods

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