Package 'dtlcor'

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Title Multiplicity Control on Drop-the-Losers Designs

Version 0.1.0

Description A tool to calculate the correlation boundary for the correlation between the response rate and the log-rank test statistic for the binary surrogate endpoint and the time-to-event primary endpoint, as well as conduct simulation studies to obtain design operating characteristics of the drop-the-losers design.

License GPL (>= 3)

Depends shiny, shinythemes, ggplot2

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`dtl_app_get_alpha_t` *Minimum significance level for the final stage under drop-the-losers (DTL) design*

Description

Get minimum significance level alpha_t (minimum of alpha_s) for the final analysis considering the ranges of response rate q and hazard ratio of responders and non-responders gamma given a pre-specified FWER alpha

Usage

```
dtl_app_get_alpha_t(n, N, q_seq, gamma_seq, alpha, fix_rho = NULL, delta)
```

Arguments

`n`	Number of patients per treatment arm at the DTL look.
`N`	Total number of patients in both selected and control arms at final analysis.
`q_seq`	A vector of response rates under the null (can be 95% CI).
`gamma_seq`	A vector of hazards ratios of responders and non-responders (can be 95% CI).
`alpha`	A pre-specified FWER.
`fix_rho`	Use fixed correlation coefficient or use theoretical upper bound to get alpha_t. If = NULL, then it uses upper bound; else if = real number between 0 and 1, then it use such number as fixed correlation coefficient.
`delta`	Least difference to decide superiority of high dose.

Value

A list of two data frames for minimum significance level alpha_t and significance level alpht_s given all combinations of q_seq and gamma_seq.

Examples

```
# Inputs
n         = 80
N         = 152
q_seq     = seq(0.19, 0.32, 0.01)
gamma_seq = seq(0.14, 0.34, 0.01)
alpha     = 0.025
delta     = 0.05

# Use fixed correlation coefficient
```

```
dtl_app_get_alpha_t(n, N, q_seq, gamma_seq, alpha, fix_rho = 1, delta)

# Use theoretical upper bound
dtl_app_get_alpha_t(n, N, q_seq, gamma_seq, alpha, fix_rho = NULL, delta)
```

`dtl_app_get_alpha_t_sim` *Numerical minimum significance level for the final stage under drop-the-losers (DTL) design*

Description

Get numerical minimum significance level alpha_t (minimum of alpha_s) for the final analysis considering the ranges of response rate q and hazard ratio of responders and non-responders gamma given a pre-specified FWER alpha

Usage

```
dtl_app_get_alpha_t_sim(
  nsim = 1e+05,
  n,
  N,
  q_seq,
  gamma_seq,
  alpha,
  fix_rho = NULL,
  sel_g_func = sel_g_func_default,
  ...
)
```

Arguments

`nsim`	Number of replicates.
`n`	Number of patients per treatment arm at the DTL look
`N`	Total number of patients in both selected and control arms at final analysis.
`q_seq`	A vector of response rates under the null (can be 95% CI).
`gamma_seq`	A vector of hazards ratios of responders and non-responders (can be 95% CI).
`alpha`	A pre-specified FWER.
`fix_rho`	Use fixed correlation coefficient or use theoretical upper bound to get alpha_t. If = NULL, then it uses upper bound; else if = real number between 0 and 1, then it use such number as fixed correlation coefficient.
`sel_g_func`	Arm-select function. The default function is sel_g_func_default(W_2, W_1, delta). Users can define their own arm-select function. The format of the function must be function_name(W_2, W_1, ...). The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility).
`...`	Other arguments from sel_g_func.

Value

A list of two data frames for numerical minimum significance level alpha_t and significance level alpht_s given all combinations of q_seq and gamma_seq.

Examples

```
# Inputs
set.seed(1000)
nsim      = 100000
n         = 80
N         = 152
q_seq     = seq(0.19, 0.32, 0.01)
gamma_seq = seq(0.14, 0.34, 0.01)
alpha     = 0.025
delta     = 0.05

# Use fixed correlation coefficient
dtl_app_get_alpha_t_sim(nsim, n, N, q_seq, gamma_seq, alpha,
                        fix_rho = 1, delta = delta)

# Use theoretical upper bound
dtl_app_get_alpha_t_sim(nsim, n, N, q_seq, gamma_seq, alpha,
                        fix_rho = NULL, delta = delta)
```

---

dtl_app_sim *Simulation study for drop-the-losers (DTL) trial.*

Description

Simulation study for a trial based on the DTL design

Usage

```
dtl_app_sim(
  nsim,
  alpha_t,
  D,
  N,
  n,
  mPFS,
  q,
  gamma,
  drop_rate,
  enroll,
  interim_t,
  sel_g_func = sel_g_func_default,
```

```
  ...
)
```

Arguments

nsim	Number of replicates.
alpha_t	significance level for the final stage (recommend to use minimum significance level alpha_t to control family-wise type I error rate).
D	Total number of events.
N	Total number of patients in both selected and control arms at final analysis.
n	Number of patients per treatment arm at the DTL look.
mPFS	A 3-entry vector of median progression-free survival times (in days) for control, low dose and high dose arms.
q	A 3-entry vector of response rates under the null.
gamma	Hazards ratio of responders and non-responders.
drop_rate	Annual drop-out rate.
enroll	Annual enrollment rate.
interim_t	A vector of information fractions of final stage.
sel_g_func	Arm-select function. The default function is sel_g_func_default(W_2, W_1, delta). Users can define their own arm-select function. The format of the function must be function_name(W_2, W_1, ...). The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility).
...	Other arguments from sel_g_func.

Value

A one row data frame of simulation results, including the parameter settings, the O'Brien-Fleming boundaries for interim and final analyses: c.1, c.2, the overall censoring rate: cen_rate, the mean study duration: dur, the probability of selecting high dose / low dose / no dose: prob_sel_2, prob_sel_1, prob_sel_0, the probability of rejecting H_1 or H_2: rej_12, the probability of rejecting H_1 only: rej_1, the probability of rejecting H_2 only: rej_2.

Examples

```
# Inputs
set.seed(1000)
nsim        = 1000
alpha_t     = 0.018
D           = 162
N           = 152
n           = 80
mPFS        = c(180, 276, 300)
q           = c(0.2, 0.4, 0.5)
mPFS_null   = rep(180, 3)
q_null      = rep(0.2, 3)
gamma       = 0.15
```

```
drop_rate   = 0.05
enroll      = 20 * 12
interim_t   = c(0.5, 1)
delta       = 0.05

# Type I Error
dtl_app_sim(nsim, alpha_t, D, N, n, mPFS_null, q_null, gamma, drop_rate,
            enroll, interim_t, delta = delta)

# Power
dtl_app_sim(nsim, alpha_t, D, N, n, mPFS, q, gamma, drop_rate, enroll,
            interim_t, delta = delta)
```

`dtl_app_sim_single` *Simulate a single drop-the-losers (DTL) trial.*

Description

Simulate a single trial based on the DTL design

Usage

```
dtl_app_sim_single(
  D,
  N,
  n,
  mPFS,
  q,
  gamma,
  drop_rate,
  enroll,
  interim_t,
  sel_g_func = sel_g_func_default,
  ...
)
```

Arguments

`D`	Total number of events.
`N`	Total number of patients in both selected and control arms at final analysis.
`n`	Number of patients per treatment arm at the DTL look.
`mPFS`	A 3-entry vector of median progression-free survival times for control, low dose and high dose arms (assume exponential time-to-event outcome for all arms and the conditional distribution for responders and non-responders can be uniquely identified given q and gamma).

q	A 3-entry vector of response rates under the null.
gamma	Hazards ratio of responders and non-responders.
drop_rate	Annual drop-out rate.
enroll	Annual Enrollment rate.
interim_t	A vector of information fractions of final stage.
sel_g_func	Arm-select function. The default function is sel_g_func_default(W_2, W_1, delta). Users can define their own arm-select function. The format of the function must be function_name(W_2, W_1, ...). The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility).
...	Other arguments from sel_g_func.

Value

A list including (1) a data frame of response rates of low dose and high dose W_1, W_2 and the log-rank test statistics Z_jk at kth interim analysis if the jth arm is selected at DTL look; (2) data frames of simulated data at DTL look; (3) data frames of simulated data at interim or final analyses.

Examples

```
# Inputs
set.seed(1000)
D           = 162
N           = 152
n           = 80
mPFS        = c(180, 276, 300)
q           = c(0.2, 0.4, 0.5)
gamma       = 0.15
drop_rate   = 0.05
enroll      = 20 * 12
interim_t   = c(0.5, 1)
delta       = 0.05

# Run function
dtl_app_sim_single(D, N, n, mPFS, q, gamma, drop_rate, enroll, interim_t, delta = delta)
```

---

dtl_cor_the_PH_upper_bound

Theoretical upper bound of correlation coefficient between time-to-event primary endpoint and binary surrogate endpoint

---

Description

Get theoretical upper bound of correlation coefficient

Usage

```
dtl_cor_the_PH_upper_bound(tau_k, pi_ar = 0.5, q, gamma)
```

Arguments

tau_k	Equals n/n_k, where n is the number of patients per treatment arm at the DTL look and n_k is the number of patients in both selected and control arms at the kth interim analysis.
pi_ar	Allocation rate of treatment and control (0.5 by default)
q	Response rate under the null
gamma	Hazards ratio of responders and non-responders

Value

Theoretical upper bound of correlation coefficient

Examples

```
dtl_cor_the_PH_upper_bound(tau_k = 0.4, pi_ar = 0.5, q = 0.3, gamma = 0.2)
```

---

dtl_get_alpha_s *Significance level given a fixed correlation coefficient for the final stage under drop-the-losers (DTL) design*

Description

Get significant level alpha_s based on a pre-specified FWER alpha given a fixed correlation coefficient for the final stage (reverse calculation of dtl_tier_the())

Usage

```
dtl_get_alpha_s(n, t, rho, q, alpha, delta)
```

Arguments

n	Sample size per arm at DTL look
t	A vector of information fraction of final stage
rho	Fixed correlation coefficient
q	Response rate under the null
alpha	A pre-specified FWER
delta	Least difference to decide superiority of high dose

Value

Significance level alpha_s for the final stage

Examples

```
# Without interim analysis
dtl_get_alpha_s(n = 80, t = 1, rho = 0.4, q = 0.3, alpha = 0.025, delta = 0.05)
```

`dtl_get_alpha_s_sim` *Numerical significance level given a fixed correlation coefficient for the final stage under drop-the-losers (DTL) design*

Description

Get the numerical significant level alpha_s based on a pre-specified FWER alpha given a fixed correlation coefficient for the final stage by simulation (reverse calculation of dtl_tier_sim())

Usage

```
dtl_get_alpha_s_sim(
  nsim = 1e+05,
  n,
  t,
  rho,
  q,
  alpha,
  sel_g_func = sel_g_func_default,
  ...
)
```

Arguments

`nsim`	Number of replicates
`n`	Sample size per arm at DTL look
`t`	A vector of information fraction of final stage
`rho`	Fixed correlation coefficient
`q`	Response rate under the null
`alpha`	A pre-specified FWER
`sel_g_func`	Arm-select function. The default function is sel_g_func_default(W_2, W_1, delta). Users can define their own arm-select function. The format of the function must be function_name(W_2, W_1, ...). The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility).
`...`	Other arguments from sel_g_func.

Value

Significance level alpha_s for the final stage

Examples

```
# Without interim analysis
dtl_get_alpha_s_sim(nsim = 100000, n = 80, t = 1, rho = 0.4, q = 0.3,
                    alpha = 0.025, delta = 0.05)
```

dtl_shiny *Shiny app of drop-the-losers (DTL) design*

Description

Interactive shiny app of drop-the-losers (DTL) design

Usage

```
dtl_shiny(appname = "shiny")
```

Arguments

appname	Default is "shiny". Do not change it since there is only one shiny app in the package

Value

The shiny app of DTL design which includes three panels:(1) family-wise type I error rate (FWER) given fixed rho; (2) correlation coefficient boundary for rho (rho_s); (3) adjusted significance level in real application (alpha_t). The first two panels show the graphs of change of the FWER and the rho_s as the change of some related parameters. The corresponding tables of the graphs are also shown. In the last panel, the table of the significance levels alpha_s based on all possible values of response rate q and hazard ratio of responders and non-responders gamma and the resulting minimum or called adjusted significance level are shown.

Examples

```
# run dtl_shiny()
```

dtl_sim_stat *Generate normal approximated test statistics for drop-the-losers (DTL) design*

Description

Generate normal approximated test statistics for drop-the-losers (DTL) design

Usage

```
dtl_sim_stat(nsim, n, q, t, rho)
```

Arguments

nsim	Number of replicates
n	Sample size per arm at DTL look
q	Response rate under the null
t	A vector of information fraction of final stage
rho	Fixed correlation coefficient

Value

Data frame of the simulated test statistics

Examples

```
dtl_sim_stat(nsim = 1000, n = 80, q = 0.3, t = c(0.3, 1), rho = c(0.5, 0.3))
```

---

dtl_tier_sim *Simulated family-wise type I error rate (FWER) given a fixed correlation coefficient under drop-the-losers (DTL) design*

Description

Get the simulated FWER alpha given fixed correlation coefficient

Usage

```
dtl_tier_sim(nsim, n, t, rho, q, alpha_s, sel_g_func = sel_g_func_default, ...)
```

Arguments

nsim	Number of replicates
n	Sample size per arm at DTL look
t	A vector of information fraction of final stage
rho	Fixed correlation coefficient
q	Response rate under the null
alpha_s	Significance level for the final stage
sel_g_func	Arm-select function. The default function is sel_g_func_default(W_2, W_1, delta). Users can define their own arm-select function. The format of the function must be function_name(W_2, W_1, ...). The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility).
...	Other arguments from sel_g_func.

Value

Simulated FWER alpha

Examples

```
# Without interim analysis
dtl_tier_sim(nsim = 1000, n = 80, t = 1, rho = 0.4, q = 0.3,
             alpha_s = 0.025, delta = 0.05)

# With interim analysis
dtl_tier_sim(nsim = 1000, n = 80, t = c(0.5, 1), rho = c(0.4, 0.2), q = 0.3,
             alpha_s = 0.025, delta = 0.05)
```

---

dtl_tier_the *Theoretical family-wise type I error rate (FWER) given a fixed correlation coefficient under drop-the-losers (DTL) design*

Description

Get the theoretical FWER alpha given fixed correlation coefficient

Usage

```
dtl_tier_the(n, t, rho, q, alpha_s, delta)
```

Arguments

n	Sample size per arm at DTL look
t	A vector of information fraction of final stage
rho	Fixed correlation coefficient
q	Response rate under the null
alpha_s	Significance level for the final stage
delta	Least difference to decide superiority of high dose

Value

Theoretical FWER alpha

Examples

```
# Without interim analysis
dtl_tier_the(n = 80, t = 1, rho = 0.4, q = 0.3, alpha_s = 0.025, delta = 0.05)

# With interim analysis
dtl_tier_the(n = 80, t = c(0.5, 1), rho = c(0.4, 0.2), q = 0.3, alpha_s = 0.025, delta = 0.05)
```

`sel_g_func_default` *Default arm-select function*

Description

Default arm-select function for selecting arm to the next stage.

Usage

```
sel_g_func_default(W_2, W_1, delta)
```

Arguments

`W_2`	Response rate for arm 2 (high dose)
`W_1`	Response rate for arm 1 (low dose)
`delta`	Least difference to decide superiority of arm 2 (high dose)

Value

The function is $g(W_2, W_1; \Delta) = 2I(W_2 - W_1 - \Delta > 0) + I(W_2 - W_1 - \Delta \leq 0)$. It returns the following values: 1: arm 1 (low dose) is selected; 2: arm 2 (high dose) is selected.

Examples

```
sel_g_func_default(W_2 = 0.5, W_1 = 0.3, delta = 0.05)
```

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