

# 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 ( $\geq 3$ )

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**Author** Weibin Zhong [aut, cre],  
Jing-ou Liu [aut],  
chenguang Wang [aut]

**Maintainer** Weibin Zhong <wzhong3@gmu.edu>

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| dtl_app_get_alpha_t | <i>Minimum significance level for the final stage under drop-the-losers (DTL) design</i> |
|---------------------|------------------------------------------------------------------------------------------|

---

## 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

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

## Value

A list of two data frames for minimum significance level `alpha_t` and significance level `alph_t` 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

|                         |                                                                                                                                                                                                                                                                                                                                   |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>nsim</code>       | Number of replicates.                                                                                                                                                                                                                                                                                                             |
| <code>n</code>          | Number of patients per treatment arm at the DTL look                                                                                                                                                                                                                                                                              |
| <code>N</code>          | Total number of patients in both selected and control arms at final analysis.                                                                                                                                                                                                                                                     |
| <code>q_seq</code>      | A vector of response rates under the null (can be 95% CI).                                                                                                                                                                                                                                                                        |
| <code>gamma_seq</code>  | A vector of hazards ratios of responders and non-responders (can be 95% CI).                                                                                                                                                                                                                                                      |
| <code>alpha</code>      | A pre-specified FWER.                                                                                                                                                                                                                                                                                                             |
| <code>fix_rho</code>    | 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.                                                                                                        |
| <code>sel_g_func</code> | Arm-select function. The default function is <code>sel_g_func_default(W_2, W_1, delta)</code> . Users can define their own arm-select function. The format of the function must be <code>function_name(W_2, W_1, ...)</code> . The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility). |
| <code>...</code>        | Other arguments from <code>sel_g_func</code> .                                                                                                                                                                                                                                                                                    |

**Value**

A list of two data frames for numerical minimum significance level `alpha_t` and significance level `alpha_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 | <i>Simulate a single drop-the-losers (DTL) trial.</i> |
|--------------------|-------------------------------------------------------|

---

## 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 $k$ th 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 | <i>Significance level given a fixed correlation coefficient for the final stage under drop-the-losers (DTL) design</i> |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

---

**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 | <i>Numerical significance level given a fixed correlation coefficient for the final stage under drop-the-losers (DTL) design</i> |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------|

---

### 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

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

### 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 | <i>Simulated family-wise type I error rate (FWER) given a fixed correlation coefficient under drop-the-losers (DTL) design</i> |
|--------------|--------------------------------------------------------------------------------------------------------------------------------|

---

**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 <code>sel_g_func_default(W_2, W_1, delta)</code> . Users can define their own arm-select function. The format of the function must be <code>function_name(W_2, W_1, ...)</code> . The return values must be 1 (arm 1 is selected) or 2 (arm 2 is selected) or 0 (stop for futility). |
| ...        | Other arguments from <code>sel_g_func</code> .                                                                                                                                                                                                                                                                                    |

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 | <i>Theoretical family-wise type I error rate (FWER) given a fixed correlation coefficient under drop-the-losers (DTL) design</i> |
|--------------|----------------------------------------------------------------------------------------------------------------------------------|

---

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 | <i>Default arm-select function</i> |
|--------------------|------------------------------------|

---

**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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