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Molecularly Targeted Agent (MTA), according to the paper Phase
I/II Dose-Finding Design for Molecularly Targeted Agent: Plateau
Determination using Adaptive Randomization’, Riviere Marie-Karelle et

License GPL-3

Depends R (>= 3.4.0)

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**dfmta-package**

**Phase I/II Adaptive Dose-Finding Design for MTA**

**Description**


**Details**

The DESCRIPTION file:

- **Package:** dfmta
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- **Title:** Phase I/II Adaptive Dose-Finding Design for MTA
- **Version:** 1.7-1
- **Date:** 2020-01-31
- **Author:** Marie-Karelle Riviere and Jacques-Henri Jourdan
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- **License:** GPL-3
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- mtaBin_next
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**Author(s)**

Marie-Karelle Riviere and Jacques-Henri Jourdan

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**References**

Description

mtaBin_next is used to determine the next optimal dose to administer in a Phase I/II clinical trial for Molecularly Targeted Agent using the design proposed by Riviere et al. entitled "Phase I/II Dose-Finding Design for Molecularly Targeted Agent: Plateau Determination using Adaptive Randomization".

Usage

mtaBin_next(ngroups=1, group_cur=1, ndose, prior_tox, prior_eff, tox_max, eff_min, cohort_start, cohort, final=FALSE, method="MTA-RA", s_1=function(n_cur){0.2}, s_2=0.07, group_pat, id_dose, toxicity, tite=TRUE, efficacy, time_follow, time_eff, time_full, cycle, c_tox=0.90, c_eff=0.40, seed = 8)

Arguments

ngroups Number of groups for the dose-finding process leading to the recommendation of different dose levels. Several groups of efficacy (e.g. based on biomarker) sharing the same toxicity can be considered. The default value is set at 1.

group_cur Group number for which the estimation and the optimal dose determination is required by the function. The default value is set at 1.

ndose Number of dose levels.

prior_tox A vector of initial guesses of toxicity probabilities associated with the doses. Must be of same length as ndose.

prior_eff A vector of initial guesses of efficacy probabilities associated with the doses for group_cur. Must be of same length as ndose.

tox_max Toxicity upper bound, i.e. maximum acceptable toxicity probability.

eff_min Efficacy lower bound, i.e. minimum acceptable efficacy probability.

cohort_start Cohort size for the start-up phase.

cohort Cohort size for the model phase.

final A boolean with value TRUE if the trial is finished and the recommended dose for further phases should be given, or FALSE (default value) if the dose determination is performed for the next cohort of patients.

method A character string to specify the method for dose allocation (<= plateau determination). The default method "MTA-RA" use adaptive randomization on posterior probabilities for the plateau location. Method based on difference in efficacy probabilities is specified by "MTA-PM".

s_1 A function depending on the number of patients included used for adaptive randomization in plateau determination, only used if the estimation method chosen is "MTA-RA". The default function is function(n_cur,n)0.2.
**mtaBin_next**

- **s_2**: Cutoff value for plateau determination, only used if the estimation method chosen is "MTA-PM". Can be seen as the minimal efficacy difference of practical importance. The default value is 0.07.

- **group_pat**: A vector indicating the group number associated with each patient included in the trial.

- **id_dose**: A vector indicating the dose levels administered to each patient included in the trial. Must be of same length as **group_pat**.

- **toxicity**: A vector of observed toxicities (DLTs) for each patient included in the trial. Must be of same length as **group_pat**.

- **tite**: A boolean indicating if the efficacy is considered as a time-to-event (default value TRUE), or if it is a binary outcome (FALSE).

- **efficacy**: A vector of observed efficacies for each patient included in the trial. Must be of same length as **group_pat**. This argument is used/required only if **tite**=FALSE. The observed efficacies of patients belonging to other groups than **group_cur** should also be filled (although not used) in the same order as **group_pat** (NA can be put).

- **time_follow**: A vector of follow-up times for each patient included in the trial. Must be of same length as **group_pat**. This argument is used/required only if **tite**=TRUE.

- **time_eff**: A vector of times-to-efficacy for each patient included in the trial. If no efficacy was observed for a patient, must be filled with +Inf. Must be of same length as **group_pat**. This argument is used/required only if **tite**=TRUE.

- **time_full**: Full follow-up time window. This argument is used only if **tite**=TRUE.

- **cycle**: Minimum waiting time between two dose cohorts (usually a toxicity cycle). This argument is used only if **tite**=TRUE.

- **c_tox**: Toxicity threshold for decision rules. The default value is set at 0.90.

- **c_eff**: Efficacy threshold for decision rules. The default value is set at 0.40.

- **seed**: Seed of the random number generator. Default value is set at 8.

### Value

An object of class "mtaBin_next" is returned, consisting of determination of the next optimal dose level to administer and estimations. Objects generated by **mtaBin_next** contain at least the following components:

- **prior_tox**: Prior toxicities.
- **prior_eff**: Prior efficacies.
- **pat_incl_group**: Number of patients included.
- **n_tox_tot**: Number of observed toxicities.
- **pi**: Estimated toxicity probabilities (if the start-up ended).
- **ptox_inf**: Estimated probabilities that the toxicity probability is inferior to **tox_max** (if the start-up ended).
- **n_eff**: Number of observed efficacies.
- **resp**: Estimated efficacy probabilities (if the start-up ended).
Estimated probabilities that the efficacy probability is superior to \( \text{eff}_{\text{min}} \) (if the start-up ended).

Posterior probabilities for the plateau location.

Current Group for dose determination.

Start-up phase is ended or not.

NEXT RECOMMENDED DOSE.

Number of groups.

Maximim sample size reached.

Toxicity upper bound (if the start-up ended).

Efficacy lower bound (if the start-up ended).

Toxicity threshold (if the start-up ended).

Efficacy threshold (if the start-up ended).

Type of outcome for efficacy (time-to-event or binary).

If efficacy is a time-to-event, full follow-up time is also reminded.

If efficacy is a time-to-event, minimum waiting time between two dose cohorts (cycle) is also reminded.

Note

The "MTA-PM" method is not implemented for non-binary efficacy, as "MTA-RA" is recommended for general use.

Author(s)

Jacques-Henri Jourdan and Marie-Karelle Riviere-Jourdan <eldamjh@gmail.com>

References


See Also

\texttt{mtaBin\_sim}.

Examples

```r
prior_tox = c(0.02, 0.06, 0.12, 0.20, 0.30, 0.40)
prior_eff = c(0.12, 0.20, 0.30, 0.40, 0.50, 0.59)
group\_pat\_1 = rep(1,33)
id\_dose\_1 = c(1,1,1,2,2,2,3,3,3,4,4,4,4,4,4,5,5,5,5,5,5,6,6,6,6,3,3,3,4,4,4,3,3,3)
tox\_1 = c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0,1,0,0,0,0,0,1,0,0,0,0,0,0)
time\_follow\_1 = c(rep(7,30),6.8,5.3,5.5)
time\_eff\_1 = c(rep(+Inf,8),4,+Inf,+Inf,+Inf,3,6,+Inf,+Inf,2,+Inf,+Inf,4,5,+Inf,
+Inf,3,2,+Inf,+Inf,2,4,6,1,+Inf,5,8,+Inf,+Inf,2,1,3,6)
```
### mtaBin_sim

**Design Simulator for MTA with binary outcomes**

**Description**

`mtaBin_sim` is used to generate simulation replicates of Phase I/II clinical trial for Molecularly Targeted Agent using the design proposed by Riviere et al. entitled "Phase I/II Dose-Finding Design for Molecularly Targeted Agent: Plateau Determination using Adaptive Randomization".

---

```r
# One group, time-to-event
mta1 = mtaBin_next(ngroups=1, group_cur=1, ndose=6, prior_tox=prior_tox, prior_eff=prior_eff, tox_max=0.35, eff_min=0.20, cohort_start=3, cohort=3, method="MTA-PM", group_pat=group_pat_1, id_dose=id_dose_1, toxicity=tox_1, tite=TRUE, time_follow=time_follow_1, time_eff=time_eff_1, time_full=7, cycle=3, c_tox=0.90, c_eff=0.40)
mta1

# One group, binary
mta2 = mtaBin_next(ngroups=1, group_cur=1, ndose=6, prior_tox=prior_tox, prior_eff=prior_eff, tox_max=0.35, eff_min=0.20, cohort_start=3, method="MTA-RA", group_pat=group_pat_1, id_dose=id_dose_1, toxicity=tox_1, tite=FALSE, efficacy=eff_2, seed = 190714)
mta2

# Three groups, binary
mta3 = mtaBin_next(ngroups=3, group_cur=2, ndose=6, prior_tox=prior_tox, prior_eff=prior_eff, tox_max=0.35, eff_min=0.20, cohort_start=3, s_1=s_1, group_pat=group_pat_3, id_dose=id_dose_3, toxicity=toxicity_3, tite=FALSE, efficacy=efficacy_3)
mta3

# Dummy example, running quickly
useless = mtaBin_next(ngroups=1, group_cur=1, ndose=4, prior_tox=c(0.12,0.20,0.30,0.40), prior_eff=c(0.20,0.30,0.40,0.50), tox_max=0.35, eff_min=0.20, cohort_start=3, group_pat=rep(1,9), id_dose=c(1,1,2,2,2,2,2,2), toxicity=c(0,0,0,1,0,0,0,0), efficacy=c(0,0,0,0,1,0,1,0), tite=FALSE)
```
Usage

mtaBin_sim(ngroups=1, ndose, p_tox, p_eff, tox_max, eff_min, prior_tox, prior_eff, poisson_rate=1, n, cohort_start=3, cohort=3, tite=TRUE, time_full, method="MTA-RA", s_1=function(n_cur){0.2}, s_2=0.07, cycle, nsim, c_tox=0.90, c_eff=0.40, seed=8, threads=0)

Arguments

ngroups Number of groups for the dose-finding process leading to the recommendation of different dose levels. Several groups of efficacy (e.g. based on biomarker) sharing the same toxicity can be considered. The default value is set at 1.

ndose Number of dose levels.

p_tox A vector of the true toxicity probabilities associated with the doses.

p_eff A vector (or matrix if several groups) of the true efficacy probabilities associated with the doses.

tox_max Toxicity upper bound, i.e. maximum acceptable toxicity probability.

eff_min Efficacy upper bound, i.e. minimum acceptable efficacy probability.

prior_tox A vector of initial guesses of toxicity probabilities associated with the doses. Must be of same length as p_tox.

prior_eff A vector (or matrix if several groups) of initial guesses of efficacy probabilities associated with the doses. Must be of same length as p_eff.

poisson_rate A vector, if several groups, of the rate(s) for the Poisson process used to simulate patient arrival (for each group), i.e. expected number of arrivals per observation window. The default value is set at 1.

n Total number of patients (per groups if several) to include in the dose-finding trial.

cohort_start Cohort size for the start-up phase. The default value is set at 3.

cohort Cohort size for the model phase. The default value is set at 3.

tite A boolean indicating if the efficacy is considered as a time-to-event (default value TRUE), or if it is a binary outcome (FALSE).

time_full Full follow-up time window. This argument is used only if tite=TRUE.

method A character string to specify the method for dose allocation ("MTA-RA") for adaptive randomization on posterior probabilities for the plateau location. Method based on difference in efficacy probabilities is specified by "MTA-PM".

s_1 A function depending on the number of patients included used for adaptive randomization in plateau determination, only used if the estimation method chosen is "MTA-RA". The default function is function(n_cur){0.2}.

s_2 Cutoff for plateau determination, only used if the estimation method chosen is "MTA-PM". Can be seen as the minimal efficacy difference of practical importance. The default value is 0.07.

cycle Minimum waiting time between two dose cohorts (usually a toxicity cycle). This argument is used only if tite=TRUE.
nsim  Number of simulations.
c_tox  Toxicity threshold for decision rules. The default value is set at 0.90.
c_eff  Efficacy threshold for decision rules. The default value is set at 0.40.
seed  Seed of the random number generator. Default value is set at 8.
threads  Number of threads to use to do the computations. If 0, it uses as many threads as available processors.

Value

An object of class "mtaBin_sim" is returned, consisting of the operating characteristics of the design specified. Objects generated by mtaBin_sim contain at least the following components:

p_tox  True toxicities.
p_eff  True efficacies (for each group).
prior_tox  Prior toxicities.
prior_eff  Prior efficacies (for each group).
rec_dose  Percentage of Selection (for each group).
n_pat_dose  Number of patients at each dose (for each group).
n_tox  Number of toxicities at each dose (for each group).
n_eff  Number of efficacies at each dose (for each group).
inconc  Percentage of inclusive trials (for each group).
method  Allocation method.
nsim  Number of simulations.
n_pat_tot  Total patients accrued.
tox_max  Toxicity upper bound.
eff_min  Efficacy lower bound.
poisson_rate  Rate for Poisson process.
c_tox  Toxicity threshold.
c_eff  Efficacy threshold.
cohort_start  Cohort size start-up phase.
cohort  Cohort size model phase.
tite  Type of outcome for efficacy (time-to-event or binary).
time_full  If efficacy is a time-to-event, full follow-up time is also reminded.
cycle  If efficacy is a time-to-event, minimum waiting time between two dose cohorts (cycle) is also reminded.
duration  If efficacy is a time-to-event, trial mean duration is also returned.

Note

The "MTA-PM" method is not implemented for non-binary efficacy, as "MTA-RA" is recommended for general use.
Author(s)
Jacques-Henri Jourdan and Marie-Karelle Riviere-Jourdan <eldamjh@gmail.com>

References

See Also

Examples

```r
p_tox_sc1 = c(0.005, 0.01, 0.02, 0.05, 0.10, 0.15)
p_eff_sc1_g1 = c(0.01, 0.10, 0.30, 0.50, 0.80, 0.80)
p_tox_sc2 = c(0.01, 0.05, 0.10, 0.25, 0.50, 0.70)
p_eff_sc2_g2 = matrix(c(0.40, 0.01, 0.40, 0.02, 0.40, 0.05, 0.40, 0.10, 0.40,
                        0.35, 0.40, 0.55), nrow=2)
prior_tox = c(0.02, 0.06, 0.12, 0.20, 0.30, 0.40)
prior_eff = c(0.12, 0.20, 0.30, 0.40, 0.50, 0.59)
prior_eff2 = rbind(prior_eff, prior_eff)
s_1=function(n_cur){0.2}
n=60

# With only one group and efficacy as time-to-event
sim1 = mtaBin_sim(ngroups=1, ndose=6, p_tox= p_tox_sc1, p_eff= p_eff_sc1_g1,
                  tox_max=0.35, eff_min=0.20, prior_tox=prior_tox, prior_eff= prior_eff,
                  poisson_rate=0.28, n=60, cohort_start=3, cohort=3, tite=TRUE,
                  time_full=7, cycle=3, nsim=1)
sim1

# With only one group and efficacy binary
sim2 = mtaBin_sim(ngroups=1, ndose=6, p_tox= p_tox_sc1, p_eff= p_eff_sc1_g1,
                  tox_max=0.35, eff_min=0.20, prior_tox=prior_tox, prior_eff= prior_eff,
                  n=n, cohort_start=3, cohort=3, tite=FALSE, method="MTA-RA",
                  s_1=function(n_cur)(0.2*(1-n_cur/n)), nsim=1)
sim2

# With only two groups and efficacy as time-to-event
sim3 = mtaBin_sim(ngroups=2, ndose=6, p_tox= p_tox_sc2, p_eff= p_eff_sc2_g2,
                  tox_max=0.35, eff_min=0.20, prior_tox=prior_tox,
                  prior_eff= prior_eff2, poisson_rate=c(0.40,0.25) , n=60,
                  cohort_start=3, cohort=3, tite=TRUE, time_full=7,
                  method="MTA-PM", s_2=0.07, cycle=3, nsim=1, c_tox=0.90, c_eff=0.40)
sim3
```
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