Package 'dfmta'

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Type Package

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

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Description Phase I/II adaptive dose-finding design for single-agent 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 al. (2016) <doi:10.1177/0962280216631763>.

License GPL-3

Depends R (>= 3.4.0)

LinkingTo RcppArmadillo (>= 0.7.100.3.1), BH (>= 1.55), RcppProgress (>= 0.2.1), Rcpp

NeedsCompilation yes

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Details

The DESCRIPTION file:

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Authors@R:	c(person(given = "Marie-Karelle", family = "Riviere", role = "aut"), person(given = "Jacques-Henri", family =
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References

Riviere, M-K., Yuan, Y., Jourdan, J-H., Dubois, F., and Zohar, S. Phase I/II Dose-Finding Design for Molecularly Targeted Agent: Plateau Determination using Adaptive Randomization.

mtaBin_next *Optimal dose determination for MTA with binary outcomes*

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}.

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	Tocixity 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).

1-qeff_inf	Estimated probabilities that the efficacy probability is superior to eff_min (if the start-up ended).
proba_tau	Posterior probabilities for the plateau location.
group_cur	Current Group for dose determination.
in_startup	Start-up phase is ended or not.
cdose	NEXT RECOMMENDED DOSE.
ngroups	Number of groups.
final	Maximim sample size reached.
method	Allocation method.
tox_max	Toxicity upper bound (if the start-up ended).
eff_min	Efficacy lower bound (if the start-up ended).
c_tox	Toxicity threshold (if the start-up ended).
c_eff	Efficacy threshold (if the start-up ended).
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.

Note

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

Author(s)

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References

Riviere, M-K., Yuan, Y., Jourdan, J-H., Dubois, F., and Zohar, S. Phase I/II Dose-Finding Design for Molecularly Targeted Agent: Plateau Determination using Adaptive Randomization.

See Also

mtaBin_sim.

Examples

```
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(1,1,1,2,2,2,3,3,3,4,4,4,5,5,5,4,4,4,5,5,5,6,6,6,3,3,3,4,4,4,3,3,3)
tox_1 = c(0,0,0,0,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0,0,1,1,0,0,0,0,0,1,0,0,0,0)
time_follow_1 = c(rep(7,30),6.8,5,3.5)
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)
```

```
eff_2 = c(0,0,0,0,0,0,0,0,1,0,0,0,1,1,0,0,1,0,0,1,0,0,1,1,0,1,0,0,1,1)
group_pat_3 = c(1,2,3,2,1,2,3,1,2,3,3,2,2,1,3,1,2,3,1,2,3,3,3,2,1,1,2,1,2,2)
id_dose_3 = c(1,1,1,1,1,1,1,1,2,1,2,2,2,2,2,2,3,2,2,3,3,3,3,3,1,1,2,1,2,2)
toxicity_3 = c(0,0,0,0,0,0,0,0,0,0,0,0,0,1,0,0,0,0,0,1,0,0,1,0,0,0,0,0,0,0)
efficacy_3 = c(NA,0,NA,0,NA,1,NA,NA,0,NA,NA,1,0,NA,NA,NA,0,NA,NA,1,NA,NA,NA,
0,NA,NA,0,NA,1,1)
s_1=function(n_cur){0.2*(1-n_cur/60)}


# 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,
       cohort=3, final = TRUE, 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,
       cohort=3, final = FALSE, 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, cohort=3,
          group_pat=rep(1,9), id_dose=c(1,1,1,2,2,2,2,2),
          toxicity=c(0,0,0,1,0,0,0,0,0), efficacy=c(0,0,0,0,0,1,0,1,0), tite=FALSE)
```

`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".

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 lower 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 (<=> 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){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	Tocixity 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)

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References

Riviere, M-K., Yuan, Y., Jourdan, J-H., Dubois, F., and Zohar, S. Phase I/II Dose-Finding Design for Molecularly Targeted Agent: Plateau Determination using Adaptive Randomization.

See Also

mtaBin_next.

Examples

```
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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