Package 'bfboinet'

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Type Package

Title Backfill Bayesian Optimal Interval Design Using Efficacy and Toxicity

Version 0.4.0

Description The backfill Bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization (BF-BOIN-ET) design is a novel clinical trial design to allow patients to be backfilled at lower doses during a dose-finding trial while prioritizing the dose-escalation cohort to explore a higher dose. The advantages compared to the other designs in terms of the percentage of correct optimal dose (OD) selection, reducing the sample size, and shortening the duration of the trial, in various realistic setting.

License GPL-3

Encoding UTF-8

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NeedsCompilation no

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Contents

`get.oc.backboinet` *backboinet*

Description

Obtain the operating characteristics of the backfill bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization within fixed scenarios

Usage

```
get.oc.backboinet(
  target_T = 0.3,
  toxprob,
  target_E = 0.25,
  effprob,
  n.dose,
  startdose,
  ncohort,
  cohortsize,
  pT.saf = 0.6 * target_T,
  pT.tox = 1.4 * target_T,
  pE.saf = 0.6 * target_E,
  alpha.T1 = 0.5,
  alpha.E1 = 0.5,
  tau.T,
  tau.E,
  te.corr = 0.2,
  gen.event.time = "weibull",
  accrual,
  gen.enroll.time = "uniform",
  n.elimination = 6,
  stopping.npts = 12,
  suspend = 0,
  stopping.prob.T = 0.95,
  stopping.prob.E = 0.9,
  ppsi01 = 0,
  ppsi00 = 40,
  ppsi11 = 60,
  ppsi10 = 100,
  n.sim = 1000,
  seed.sim = 100
)
```

Arguments

`target_T`	Target toxicity probability. The default value is `target_T=0.3`. When observing 1 DLT out of 3 patients and the target DLT rate is between 0.25 and 0.279, the decision is to stay at the current dose due to a widely accepted practice.

toxprob	Vector of true toxicity probability.
target_E	The minimum required efficacy probability. The default value is target_E=0.25.
effprob	Vector of true efficacy probability.
n.dose	Number of dose.
startdose	Starting dose. The lowest dose is generally recommended.
ncohort	Number of cohort.
cohortsize	Cohort size.
pT.saf	Highest toxicity probability that is deemed sub-therapeutic such that dose-escalation should be pursued. The default value is pT.saf=target_T*0.6.
pT.tox	Lowest toxicity probability that is deemed overly toxic such that dose de-escalation is needed. The default value is pT.tox=target_T*1.4.
pE.saf	Minimum probability deemed efficacious such that the dose levels with less than delta1 are considered sub-therapeutic. The default value is pE.saf=target_E*0.6.
alpha.T1	Probability that toxicity event occurs in the late half of toxicity assessment window. The default value is alpha.T1=0.5.
alpha.E1	Probability that efficacy event occurs in the late half of assessment window. The default value is alpha.E1=0.5.
tau.T	Toxicity assessment windows (months).
tau.E	Efficacy assessment windows (months).
te.corr	Correlation between toxicity and efficacy probability, specified as Gaussian copula parameter. The default value is te.corr=0.2.
gen.event.time	Method to generate the time to first toxicity and efficacy outcome. Weibull distribution is used when gen.event.time ="weibull". Uniform distribution is used when gen.event.time="uniform". The default value is gen.event.time="weibull".
accrual	Accrual rate (months) (patient accrual rate per month).
gen.enroll.time	Method to generate enrollment time. Uniform distribution is used when gen.enroll.time="uniform". Exponential distribution is used when gen.enroll.time="exponential". The default value is gen.enroll.time="uniform".
n.elimination	a minimum sample size for dose elimination. If the number of patients treated at the current dose reaches n.elimination and meet elimination dose level criteria, eliminate current dose level and higher doses when meet toxicity criteria and eliminate current dose level when meet efficacy criteria. The default value is n.elimination=6.
stopping.npts	Early study termination criteria for the number of patients in the dose-escalation and backfill cohorts. If the number of patients at the current dose reaches this criteria and the same dose level is recommended as the next dose level, the study is terminated. The default value is stopping.npts=12.
suspend	The suspension rule that holds off the decision on dose allocation for the dose-escalation cohort until sufficient toxicity information is available. For example, setting as 0.33 which means one-third of the patients had not completed the toxicity evaluation at the current dose level in the dose escalation cohort. The

default value `suspend=0` essentially turns off this type of suspending rule, that is all patients should complete the toxicity evaluation at the current dose level in the dose escalation cohort

`stopping.prob.T`
: Early study termination criteria for toxicity, taking a value between 0 and 1. If the posterior probability that toxicity outcome is less than the target toxicity probability (`target_T`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.T=0.95`.

`stopping.prob.E`
: Early study termination criteria for efficacy, taking a value between 0 and 1. If the posterior probability that efficacy outcome is less than the minimum efficacy probability (`target_E`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.E=0.90`.

`ppsi01`
: Score for toxicity=yes and efficacy=no in utility defined by scoring.The default value is `psi01=0`.

`ppsi00`
: Score for toxicity=no and efficacy=no in utility defined by scoring. The default value is `psi00=40`.

`ppsi11`
: Score for toxicity=yes and efficacy=yes in utility defined by scoring. The default value is `psi11=60`.

`ppsi10`
: Score for toxicity=no and efficacy=yes in utility defined by scoring. The default value is `psi10=100`.

`n.sim`
: Number of simulated trial. The default value is `n.sim=1000`.

`seed.sim`
: Seed for random number generator. The default value is `seed.sim=100`.

Details

The `backboinet` is a function which generates the operating characteristics of the backfill bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization by a simulation study. Users can specify a variety of study settings to simulate studies. The operating characteristics of the design are summarized by the percentage of times that each dose level was selected as optimal biological dose and the average number of patients who were treated at each dose level. The percentage of times that the study was terminated and the expected study duration are also provided.

Value

The `backboinet` returns a list containing the following components:

`toxprob`
: True toxicity probability.

`effprob`
: True efficacy probability.

`phi`
: Target toxicity probability.

`delta`
: Target efficacy probability.

`lambda1`
: Lower toxicity boundary in dose escalation/de-escalation.

`lambda2`
: Upper toxicity boundary in dose escalation/de-escalation.

`eta1`
: Lower efficacy boundary in dose escalation/de-escalation.

`tau.T`
: Toxicity assessment windows (months).

tau.E	Efficacy assessment windows (months).
suspend	The suspension rule that holds off the decision on dose allocation for the dose-escalation cohort until sufficient toxicity information is available.
accrual	Accrual rate (months) (patient accrual rate per month).
n.patient	Average number of patients who were treated at each dose level in dose-esclation and backfill cohorts
n.bpatient	Average number of back filled patients who were treated at each dose level
n.tox.patient	Average number of patients who experienced toxicity at each dose level in dose-esclation and backfill cohorts
n.eff.patient	Average number of patients who experienced efficacy at each dose level in dose-esclation and backfill cohorts
n.tox.bpatient	Average number of patients who experienced toxicity at each dose level in back-fill cohort
n.eff.bpatient	Average number of patients who experienced efficacy at each dose level in back-fill cohort
prop.select	Percentage of times that each dose level was selected as optimal biological dose.
prop.stop	Percentage of times that the study was terminated.
duration	Expected study duration (months)
totaln	Total patients
data.obs.n	Record the number of patients in each dose level within the simulations during the trial
obd	Record the optimal dose in each simulation during the trial
backfilltimes	Record how may times we back-filled during the trial
backfillcount	Record the number of back-filled patients in dose level within the simulations during the trial
PCS	The percentage of trials that the optimal dose was correctly selected.
PCA	The percentage of patients that were correctly allocated to the optimal dose.
PTS	The percentage of toxic doses selection.
PTA	The percentage of patients who were allocated to toxic doses.

References

BF-BOIN-ET: A backfill Bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization.

Examples

```
target_T=0.3
target_E=0.25
toxprob=c(0.03,0.05,0.2,0.22,0.45)
effprob=c(0.05,0.1,0.5,0.68,0.7)

get.oc.backboinet(target_T=target_T, toxprob=toxprob,target_E=target_E,
```

```
effprob=effprob,n.dose=5,startdose=1,ncohort=10,cohortsize=3,
pT.saf=0.6 * target_T,pT.tox = 1.4 * target_T,pE.saf = 0.6 * target_E,
alpha.T1=0.5,alpha.E1=0.5,tau.T=1,tau.E=1,te.corr=0.2,
gen.event.time="weibull",accrual=3,gen.enroll.time="uniform",n.elimination=6,
stopping.npts=12,suspend=0,stopping.prob.T=0.95,stopping.prob.E=0.90,
ppsi01=0,ppsi00=40,ppsi11=60,ppsi10=100,n.sim=2,seed.sim=100)
```

`get.oc.backboinetr` *backboinetr*

Description

Obtain the operating characteristics of the backfill bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization within random scenarios

Usage

```
get.oc.backboinetr(
  target_T = 0.3,
  target_Tr = 0.359,
  target_E = 0.25,
  target_Er = 0.197,
  n.dose,
  startdose,
  ncohort,
  cohortsize,
  pT.saf = 0.6 * target_T,
  pT.tox = 1.4 * target_T,
  pE.saf = 0.6 * target_E,
  alpha.T1 = 0.5,
  alpha.E1 = 0.5,
  tau.T,
  tau.E,
  te.corr = 0.2,
  gen.event.time = "weibull",
  accrual,
  gen.enroll.time = "uniform",
  n.elimination = 6,
  stopping.npts = 12,
  suspend = 0,
  stopping.prob.T = 0.95,
  stopping.prob.E = 0.9,
  ppsi01 = 0,
  ppsi00 = 40,
  ppsi11 = 60,
  ppsi10 = 100,
```

```
  n.sim = 10000,
  seed.sim = 30
)
```

Arguments

target_T	Target toxicity probability. The default value is target_T=0.3. When observing 1 DLT out of 3 patients and the target DLT rate is between 0.25 and 0.279, the decision is to stay at the current dose due to a widely accepted practice.
target_Tr	The upper boundary for the toxicity when generating the random scenarios. The default value is target_Tr=0.359.
target_E	The minimum required efficacy probability. The default value is target_E=0.25.
target_Er	The lower boundary for the efficacy when generating the random scenarios. The default value is target_Er=0.197.
n.dose	Number of dose.
startdose	Starting dose. The lowest dose is generally recommended.
ncohort	Number of cohort.
cohortsize	Cohort size.
pT.saf	Highest toxicity probability that is deemed sub-therapeutic such that dose-escalation should be pursued. The default value is pT.saf=target_T*0.6.
pT.tox	Lowest toxicity probability that is deemed overly toxic such that dose de-escalation is needed. The default value is pT.tox=target_T*1.4.
pE.saf	Minimum probability deemed efficacious such that the dose levels with less than delta1 are considered sub-therapeutic. The default value is pE.saf=target_E*0.6.
alpha.T1	Probability that toxicity event occurs in the late half of toxicity assessment window. The default value is alpha.T1=0.5.
alpha.E1	Probability that efficacy event occurs in the late half of assessment window. The default value is alpha.E1=0.5.
tau.T	Toxicity assessment windows (months).
tau.E	Efficacy assessment windows (months).
te.corr	Correlation between toxicity and efficacy probability, specified as Gaussian copula parameter. The default value is te.corr=0.2.
gen.event.time	Method to generate the time to first toxicity and efficacy outcome. Weibull distribution is used when gen.event.time ="weibull". Uniform distribution is used when gen.event.time="uniform". The default value is gen.event.time="weibull".
accrual	Accrual rate (months) (patient accrual rate per month).
gen.enroll.time	Method to generate enrollment time. Uniform distribution is used when gen.enroll.time="uniform". Exponential distribution is used when gen.enroll.time="exponential". The default value is gen.enroll.time="uniform".
n.elimination	a minimum sample size for dose elimination. If the number of patients treated at the current dose reaches n.elimination and meet elimination dose level criteria, eliminate current dose level and higher doses when meet toxicity criteria and eliminate current dose level when meet efficacy criteria. The default value is n.elimination=6.

`stopping.npts` Early study termination criteria for the number of patients in the dose-escalation and backfill cohorts. If the number of patients at the current dose reaches this criteria and the same dose level is recommended as the next dose level, the study is terminated. The default value is `stopping.npts=12`.

`suspend` the suspension rule that holds off the decision on dose allocation for the dose-escalation cohort until sufficient toxicity information is available. For example, setting as 0.33 which means one-third of the patients had not completed the toxicity evaluation at the current dose level in the dose escalation cohort. The default value `suspend=0` essentially turns off this type of suspending rule, that is all patients should complete the toxicity evaluation at the current dose level in the dose escalation cohort

`stopping.prob.T` Early study termination criteria for toxicity, taking a value between 0 and 1. If the posterior probability that toxicity outcome is less than the target toxicity probability (`target_T`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.T=0.95`.

`stopping.prob.E` Early study termination criteria for efficacy, taking a value between 0 and 1. If the posterior probability that efficacy outcome is less than the minimum efficacy probability (`target_E`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.E=0.90`.

`ppsi01` Score for toxicity=yes and efficacy=no in utility defined by scoring.The default value is `psi01=0`.

`ppsi00` Score for toxicity=no and efficacy=no in utility defined by scoring. The default value is `psi00=40`.

`ppsi11` Score for toxicity=yes and efficacy=yes in utility defined by scoring. The default value is `psi11=60`.

`ppsi10` Score for toxicity=no and efficacy=yes in utility defined by scoring. The default value is `psi10=100`.

`n.sim` Number of simulated trial. The default value is `n.sim=10000`.

`seed.sim` Seed for random number generator. The default value is `seed.sim=30`.

Details

The `backboinetr` is a function which generates the operating characteristics of the backfill bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization by a simulation study. Users can specify a variety of study settings to simulate studies. The operating characteristics of the design are summarized by the percentage of times that each dose level was selected as optimal biological dose and the average number of patients who were treated at each dose level. The percentage of times that the study was terminated and the expected study duration are also provided.

Value

The `backboinetr` returns a list containing the following components:

`toxprob` The random true toxicity probability.

`effprob` The random true efficacy probability.

phi	Target toxicity probability.
delta	Target efficacy probability.
target_Tr	The upper boundary for the toxicity when generating the random scenarios.
target_Er	The lower boundary for the efficacy when generating the random scenarios.
bd.true	The target optimal dose (OD) level when generating the random scenarios.
mtd.true	The maximum tolerated dose (MTD) level when generating the random scenarios.
lambda1	Lower toxicity boundary in dose escalation/de-escalation.
lambda2	Upper toxicity boundary in dose escalation/de-escalation.
eta1	Lower efficacy boundary in dose escalation/de-escalation.
tau.T	Toxicity assessment windows (months).
tau.E	Efficacy assessment windows (months).
suspend	The suspension rule that holds off the decision on dose allocation for the dose-escalation cohort until sufficient toxicity information is available.
accrual	Accrual rate (months) (patient accrual rate per month).
n.patient	Average number of patients who were treated at each dose level in dose-esclation and backfill cohorts
n.bpatient	Average number of back filled patients who were treated at each dose level
n.tox.patient	Average number of patients who experienced toxicity at each dose level in dose-esclation and backfill cohorts
n.eff.patient	Average number of patients who experienced efficacy at each dose level in dose-esclation and backfill cohorts
n.tox.bpatient	Average number of patients who experienced toxicity at each dose level in backfill cohort
n.eff.bpatient	Average number of patients who experienced efficacy at each dose level in backfill cohort
prop.select	Percentage of times that each dose level was selected as optimal biological dose.
prop.stop	Percentage of times that the study was terminated.
duration	Expected study duration (months)
totaln	Total patients
data.obs.n	Record the number of patients in each dose level within the simulations during the trial
obd	Record the optimal dose in each simulation during the trial
backfilltimes	Record how may times we back-filled during the trial
backfillcount	Record the number of back-filled patients in dose level within the simulations during the trial
PCS	The percentage of trials that the optimal dose was correctly selected.
PCA	The percentage of patients that were correctly allocated to the optimal dose.
PTS	The percentage of toxic doses selection.
PTA	The percentage of patients who were allocated to toxic doses.

References

BF-BOIN-ET: A backfill Bayesian optimal interval design using efficacy and toxicity outcomes for dose optimization.

Examples

```
target_T=0.3
target_E=0.25

get.oc.backboinetr(target_T=target_T,target_Tr=0.359,target_E=target_E,
target_Er=0.197,n.dose=5,startdose=1,ncohort=10,cohortsize=3,
pT.saf=0.6 * target_T,pT.tox = 1.4 * target_T,pE.saf = 0.6 * target_E,
alpha.T1=0.5,alpha.E1=0.5,tau.T=1,tau.E=1,te.corr=0.2,
gen.event.time="weibull",accrual=3,gen.enroll.time="uniform",n.elimination=6,
stopping.npts=12,suspend=0,stopping.prob.T=0.95,stopping.prob.E=0.90,
ppsi01=0,ppsi00=40,ppsi11=60,ppsi10=100,n.sim=2,seed.sim=30)
```

Index