Package 'bfboinet'

May 7, 2026

Type Package

Title Backfill Bayesian Optimal Interval Design Using Efficacy and Toxicity

Version 1.1.0

Description Implements the Backfill Bayesian Optimal Interval Design (BF-BOIN-ET), a novel clinical trial methodology for dose optimization that simultaneously consider both efficacy and toxicity outcome as described in (Takeda et al (2025) <doi:10.1002/pst.2470>). The package has been extended to include a seamless two-stage phase I/II trial design with backfill and joint efficacy and toxicity monitoring as described in (Takeda et al (2026) <doi:10.1002/pst.70092>).

License GPL-3

Encoding UTF-8

RoxygenNote 7.3.3

Imports Iso, copula, dplyr, tidyselect, magrittr, BOP2FE, boinet, BOIN

NeedsCompilation no

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Repository CRAN

Date/Publication 2026-04-29 06:20:02 UTC

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

Takeda, K., Zhu, J. and Hirakawa, A. (2025), BF-BOIN-ET: A Backfill Bayesian Optimal Interval Design Using Efficacy and Toxicity Outcomes for Dose Optimization. Pharmaceutical Statistics, 24: e2470. https://doi.org/10.1002/pst.2470

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)
## Not run:
```

```
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)

## End(Not run)
```

`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

Takeda, K., Zhu, J. and Hirakawa, A. (2025), BF-BOIN-ET: A Backfill Bayesian Optimal Interval Design Using Efficacy and Toxicity Outcomes for Dose Optimization. Pharmaceutical Statistics, 24: e2470. https://doi.org/10.1002/pst.2470

Examples

```
target_T=0.3
target_E=0.25
## Not run:
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)

## End(Not run)
```

---

get.oc.backboinet_rp2 *bfboinet_rp2*

Description

Obtain the operating characteristics of a seamless two-stage phase I/II trial design with backfill and joint monitoring for dose optimization within fixed scenarios

Usage

```
get.oc.backboinet_rp2(
  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,
  Nesc = 36,
  boundMTD = FALSE,
  estpt.method,
  obd.method,
  w1 = 0.33,
  w2 = 1.09,
  plow.ast = pT.saf,
  pupp.ast = pT.tox,
  qlow.ast = pE.saf/2,
  qupp.ast = target_E,
  stage1.method,
  H0,
  H1,
  nIA.sample,
  nIA = length(nIA.sample),
  method = "power",
  t1e_optimal_pars,
  lambda1_optimal_pars,
  lambda2_optimal_pars,
  grid1_optimal_pars,
  gamma1_optimal_pars,
  gamma2_optimal_pars,
  grid2_optimal_pars,
  eta1_optimal_pars,
  eta2_optimal_pars,
  grid3_optimal_pars,
  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 for stage 1.
startdose	Starting dose. The lowest dose is generally recommended.
ncohort	Number of cohort for stage 1.
cohortsize	Cohort size for stage 1.
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	to avoid allocating patients to severely toxic doses, dose elimination criteria are applied before the dose allocation decision when n treated at the current dose reaches n.elimination,it is a minimum sample size for dose elimination.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`.

Nesc — the total number of patients () in the dose-escalation cohort (Stage 1) reaches the maximum total number of patients in the dose-escalation cohort (`Nesc`). The default value is `Nesc=36`.

boundMTD — set `boundMTD=TRUE` to impose the condition: the isotonic estimate of toxicity probability for the selected MTD must be less than de-escalation boundary. The default value is `boundMTD=FALSE`.

estpt.method — Method to estimate the efficacy probability. Fractional polynomial logistic regression is used when `estpt.method="fp.logistic"`. Model averaging of multiple unimodal isotopic regression is used when `estpt.method="multi.iso"`. Observed efficacy probability is used when `estpt.method="obs.prob"`.

obd.method — Method to select the optimal biological dose. Utility defined by weighted function is used when `obd.method="utility.weighted"`. Utility defined by truncated linear function is used when `obd.method="utility.truncated.linear"`. Utility defined by scoring is used when `obd.method="utility.scoring"`. Highest estimated efficacy probability is used when `obd.method="max.effprob"`.

w1 — Weight for toxicity-efficacy trade-off in utility defined by weighted function. This must be specified when using `obd.method="utility.weighted"`. The default value is `w1=0.33`.

w2 — Weight for penalty imposed on toxic doses in utility defined by weighted function. This must be specified when using `obd.method="utility.weighted"`. The default value is `w2=1.09`.

plow.ast — Lower threshold of toxicity linear truncated function. This must be specified when using `obd.method="utility.truncated.linear"`. The default value is `plow.ast=pT.saf`.

pupp.ast — Upper threshold of toxicity linear truncated function. This must be specified when using `obd.method="utility.truncated.linear"`. The default value is `pupp.ast=pT.tox`.

qlow.ast — Lower threshold of efficacy linear truncated function. This must be specified when using `obd.method="utility.truncated.linear"`. The default value is `qlow.ast=pE.saf/2`.

qupp.ast Upper threshold of efficacy linear truncated function. This must be specified when using obd.method="utility.truncated.linear". The default value is qupp.ast=target_E.

stage1.method Method to patient assignment for backfilling patients. Pick-the-winner is used when stage1.method="PW". Equal randomization is used when stage1.method="ER".

H0 Stage 2: A numeric value for the response rate under the null hypothesis (toxicity - OR, no toxicity - OR, toxicity - no OR, no toxicity - No OR).

H1 Stage 2: A numeric value for the response rate under the alternative hypothesis.

nIA.sample Stage 2: A numeric vector representing the additional patients enrolled at each interim analysis. The value at index 'i' indicates the number of patients at interim analysis 'i'. For example, for four interim analyses with total sample sizes of 10, 15, 20, and 30, the vector would be represented as 'n = c(10, 15, 20, 30)'.

nIA Stage 2: A numeric value for the number of interim analysis. The default value is nIA=length(nIA.sample).

method Stage 2: A character string specifying the method to use for calculating cutoff values for the efficacy stopping. Options are "power" (default) or "OF" for "O'Brien-Fleming".

t1e_optimal_pars
Stage 2: Desired Type - I error rate. If specified it will only return results with type I error rate less the specified value.

lambda1_optimal_pars
Stage 2: Starting value for 'lambda' values to search.

lambda2_optimal_pars
Stage 2: Ending value for 'lambda' values to search.

grid1_optimal_pars
Stage 2: Number of 'lambda' values to consider between lambda1 and lambda2. A fine grid by 0.01 is recommended.

gamma1_optimal_pars
Stage 2: Starting value for 'gamma' values to search.

gamma2_optimal_pars
Stage 2: Ending value for 'gamma' values to search.

grid2_optimal_pars
Stage 2: Number of 'gamma' values to consider between gamma1 and gamma2. A fine grid by 0.01 is recommended.

eta1_optimal_pars
Stage 2: Starting value for 'eta' values to search.

eta2_optimal_pars
Stage 2: Ending value for 'eta' values to search.

grid3_optimal_pars
Stage 2: Number of eta values to consider between eta1 and eta2. A fine grid by 0.01 is recommended.

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 bfboinet_rp2 is a function which generates the operating characteristics of the seamless two-stage Phase I/II trial design integrating dose optimization with efficacy evaluation 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 get.oc.backboinet_rp2 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.all	Average number of patients who were treated at each dose level at stage 1 and stage 2.
nptsdosepct.all	The percentage of patients who were treated at each dose level at stage 1 and stage 2.
n.tox.patient.all	Average number of patients who experienced toxicity at each dose level at stage 1 and stage 2.
n.eff.patient.all	Average number of patients who experienced efficacy at each dose level at stage 1 and stage 2.

`n.patient.stage2`
: Average number of patients who were treated at each dose level at stage 2.

`n.bpatient`
: Average number of back filled patients who were treated at each dose level at stage 1.

`prop.select`
: Percentage of times that each dose level was selected as optimal biological dose at stage 1 and stage 2.

`MTD.select`
: Percentage of times that each dose level was selected as maximum tolerated dose at stage 1 and stage 2.

`claim.select`
: Percentage of times that each dose level was claimed efficacy at stage 1 and stage 2.

`prop.stop`
: Percentage of times that the study was terminated at stage 1.

`duration`
: Expected study duration (months) at stage 1 and stage 2.

`duration1`
: Expected study duration (months) at stage 1.

`duration2`
: Expected study duration (months) at stage 2.

`totaln`
: Total patients at stage 1 and stage 2.

`data.obs.n`
: Record the number of patients in each dose level within the simulations during the trial at stage 1 and stage 2.

`data.obs.n.stage2`
: Record the number of patients in each dose level within the simulations during the trial at stage 2.

`data.obs.n.stage1`
: Record the number of patients in each dose level within the simulations during the trial at stage 1.

`obd`
: Record the optimal dose in each simulation during the trial at stage 1 and stage 2.

`claim`
: Record the optimal dose with efficacy in each simulation during the trial at stage 1 and stage 2.

`PCS`
: The percentage of trials that the optimal dose was correctly selected at stage 1 and stage 2.

`PCC`
: The percentage of patients that efficacy were correctly allocated to the optimal dose at stage 1 and stage 2.

`PTS`
: The percentage of toxic doses selection at stage 1 and stage 2.

`PTA`
: The percentage of patients who were allocated to toxic doses at stage 1 and stage 2.

`boundary_tab.all.out`
: Futility and efficacy stopping boundaries at stage 2.

`lambda`
: Lambda values for cut-off probabilitys at stage 2.

`gamma`
: Gamma values for cut-off probability at stage 2.

`eta`
: Eta values for cut-off probability at stage 2.

References

A seamless two-stage phase I/II trial design with backfill and joint efficacy and toxicity monitoring as described in (Takeda et al (2026) <doi:10.1002/pst.70092>.

Examples

```
target_T=0.3
target_E=0.25
pttt=c(0.02, 0.05, 0.07, 0.10, 0.15)
pee=c(0.05, 0.08, 0.15, 0.30, 0.45)
#####Stage 2####;
H0=c(0.10, 0.15, 0.30, 0.45)
H1=c(0.05, 0.45, 0.15, 0.35)
nIA.sample=c(24,30,36,42,48)
nIA=length(nIA.sample)
t1e_optimal_pars=0.1
lambda1_optimal_pars=0
lambda2_optimal_pars=1
grid1_optimal_pars=101
gamma1_optimal_pars=0
gamma2_optimal_pars=1
grid2_optimal_pars=101
eta1_optimal_pars=0
eta2_optimal_pars=3
grid3_optimal_pars=301
## Not run:
get.oc.backboinet_rp2(target_T=target_T, toxprob=pttt,target_E=target_E,effprob=pee,n.dose=5,
startdose=1,ncohort=40,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,Nesc=36,
boundMTD = FALSE,estpt.method="obs.prob", obd.method="utility.scoring",
w1= 0.33, w2=1.09,plow.ast=pT.saf, pupp.ast=pT.tox, qlow.ast=pE.saf/2, qupp.ast=target_E,
stage1.method="ER",H0=H0,H1=H1,nIA.sample=nIA.sample,nIA=length(nIA.sample),
t1e_optimal_pars=t1e_optimal_pars,lambda1_optimal_pars=lambda1_optimal_pars,
lambda2_optimal_pars=lambda2_optimal_pars,grid1_optimal_pars=grid1_optimal_pars,
gamma1_optimal_pars=gamma1_optimal_pars,gamma2_optimal_pars=gamma2_optimal_pars,
grid2_optimal_pars=grid2_optimal_pars,eta1_optimal_pars=eta1_optimal_pars,
eta2_optimal_pars=eta2_optimal_pars,grid3_optimal_pars=grid3_optimal_pars,
ppsi01=0,ppsi00=40,ppsi11=60, ppsi10=100,n.sim=1,seed.sim=100)

## End(Not run)
```

`select_mtd` *select_mtd*

Description

Obtain the maximum tolerated dose (MTD) of the backfill bayesian optimal interval design using efficacy and toxicity outcomes.

Usage

```
select_mtd(
  target = 0.3,
  npts,
  ntox,
  cutoff.eli = 0.95,
  extrasafe = FALSE,
  offset = 0.05,
  p.tox = 1.4 * target,
  boundMTD = FALSE,
  n.elimination = 3
)
```

Arguments

target	Target toxicity probability. The default value is target_T=0.3.
npts	The number of patients enrolled at each dose level.
ntox	Number of patients with dose limiting toxicity (DLT).
cutoff.eli	The cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (cutoff.eli=0.95) for general use.
extrasafe	Set extrasafe=TRUE to impose a more stringent stopping rule. The default value is extrasafe=FALSE.
offset	A small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.
p.tox	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4*target.
boundMTD	set boundMTD=TRUE to impose the condition: the isotonic estimate of toxicity probability for the selected MTD must be less than de-escalation boundary. The default value is boundMTD=FALSE.
n.elimination	The sample size cutoff for elimination. The default is n.elimination=3.

Value

select_mtd() returns the selected dose.

References

1. Liu S. and Yuan, Y. (2015). Bayesian optimal interval designs for phase I clinical trials, Journal of the Royal Statistical Society: Series C , 64, 507-523. 2. Yuan, Y., Hess, K. R., Hilsenbeck, S. G., & Gilbert, M. R. (2016). Bayesian optimal interval design: a simple and well-performing design for phase I oncology trials. Clinical Cancer Research, 22(17), 4291-4301. 3. Zhou, H., Yuan, Y., & Nie, L. (2018). Accuracy, safety, and reliability of novel phase I trial designs. Clinical Cancer Research, 24(18), 4357-4364. 4. Zhou, Y., Lin, R., Kuo, Y. W., Lee, J. J., & Yuan, Y. (2021). BOIN Suite: A Software Platform to Design and Implement Novel Early-Phase Clinical Trials. JCO

Clinical Cancer Informatics, 5, 91-101. 5. Takeda K, Xia Q, Liu S, Rong A. TITE-gBOIN: Time-to-event Bayesian optimal interval design to accelerate dose-finding accounting for toxicity grades. Pharm Stat. 2022 Mar;21(2):496-506. doi: 10.1002/pst.2182. Epub 2021 Dec 3. PMID: 34862715. 6. Yuan, Y., Lin, R., Li, D., Nie, L. and Warren, K.E. (2018). Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials. Clinical Cancer Research, 24(20): 4921-4930. 7. Rongji Mu, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, Jun Yin, gBOIN: A Unified Model-Assisted Phase I Trial Design Accounting for Toxicity Grades, and Binary or Continuous End Points, Journal of the Royal Statistical Society Series C: Applied Statistics, Volume 68, Issue 2, February 2019, Pages 289–308, https://doi.org/10.1111/rssc.12263. 8. Lin R, Yuan Y. Time-to-event model-assisted designs for dose-finding trials with delayed toxicity. Biostatistics. 2020 Oct 1;21(4):807-824. doi: 10.1093/biostatistics/kxz007. PMID: 30984972; PMCID: PMC8559898. 9. Hsu C, Pan H, Mu R (2022). _UnifiedDoseFinding: Dose-Finding Methods for Non-Binary Outcomes_. R package version 0.1.9, <https://CRAN.R-project.org/package=UnifiedDoseFinding>.

Examples

```
target<-0.3
y<-c(0,0,1,2,3,0)
n<-c(3,3,6,9,9,0)
select_mtd(target=target,npts=n,ntox=y)
```

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