Package 'boinet'

August 24, 2024

Version 1.1.0

Title Conduct Simulation Study of Bayesian Optimal Interval Design with BOIN-ET Family

Description Bayesian optimal interval based on both efficacy and toxicity outcomes (BOIN-ET) design is a model-assisted oncology phase I/II trial design, aiming to establish an optimal biological dose accounting for efficacy and toxicity in the framework of dose-finding. Some extensions of BOIN-ET design are also available to allow for time-to-event efficacy and toxicity outcomes based on cumulative and pending data (time-to-event BOIN-ET: TITE-BOIN-ET), ordinal graded efficacy and toxicity outcomes (generalized BOIN-ET: gBOIN-ET), and their combination (TITE-gBOIN-ET). 'boinet' is a package to implement the BOIN-ET design family and supports the conduct of simulation studies to assess operating characteristics of BOIN-ET, TITE-BOIN-ET, gBOIN-ET, and TITE-gBOIN-ET, where users can choose design parameters in flexible and straightforward ways depending on their own application.

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Encoding UTF-8

RoxygenNote 7.3.1

Imports Iso, mfp, copula

Suggests testthat (>= 3.0.0)

Config/testthat/edition 3

NeedsCompilation no

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Repository CRAN

Date/Publication 2024-08-24 06:20:02 UTC

Contents

`boinet` *Conducting simulation study of BOIN-ET design*

Description

Bayesian optimal interval design for dose finding based on both efficacy and toxicity outcomes (BOIN-ET design) is implemented under a scenario specified. 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.

Usage

```
boinet(
  n.dose, start.dose, size.cohort, n.cohort,
  toxprob, effprob,
  phi=0.3, phi1=phi*0.1, phi2=phi*1.4, delta=0.6, delta1=delta*0.6,
  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",
  stopping.npts=size.cohort*n.cohort,
  stopping.prob.T=0.95, stopping.prob.E=0.99,
  estpt.method, obd.method,
  w1= 0.33, w2=1.09,
  plow.ast=phi1, pupp.ast=phi2, qlow.ast=delta1/2, qupp.ast=delta,
  psi00=40, psi11=60,
  n.sim=1000, seed.sim=100)
```

Arguments

`n.dose`	Number of dose.
`start.dose`	Starting dose. The lowest dose is generally recommended.
`size.cohort`	Cohort size.

n.cohort	Number of cohort.
toxprob	Vector of true toxicity probability.
effprob	Vector of true efficacy probability.
phi	Target toxicity probability. The default value is phi=0.3.
phi1	Highest toxicity probability that is deemed sub-therapeutic such that dose-escalation should be pursued. The default value is phi1=phi*0.1.
phi2	Lowest toxicity probability that is deemed overly toxic such that dose de-escalation is needed. The default value is phi2=phi*1.4.
delta	Target efficacy probability. The default value is delta=0.6.
delta1	Minimum probability deemed efficacious such that the dose levels with less than delta1 are considered sub-therapeutic. The default value is delta1=delta*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 (days).
tau.E	Efficacy assessment windows (days).
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 (days) (average number of days necessary to enroll one patient).
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".
stopping.npts	Early study termination criteria for the number of patients. If the number of patients at the current dose reaches this criteria, the study is terminated. The default value is stopping.npts=size.cohort*n.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 (phi) 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 (delta1) is larger than this criteria, the dose levels are eliminated from the study. The default value is stopping.prob.E=0.99.
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=phi1.
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=phi2.
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=delta1/2.
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=delta.
psi00	Score for toxicity=no and efficacy=no in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi00=40.
psi11	Score for toxicity=yes and efficacy=yes in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi11=60.
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 boinet is a function which generates the operating characteristics of the Bayesian Optimal Interval design based on toxicity and efficacy (BOIN-ET design) by a simulation study. Users can specify a variety of study settings to simulate studies, and choose methods to estimate the efficacy probability and to select the optimal biological dose. 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 boinet 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 (days).
tau.E	Efficacy assessment windows (days).
accrual	Accrual rate (days) (average number of days necessary to enroll one patient).
estpt.method	Method to estimate the efficacy probability.
obd.method	Method to select the optimal biological dose.
n.patient	Average number of patients who were treated at each dose level
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 and optimal biological dose was not selected.
duration	Expected study duration (days)

References

Takeda K, Taguri M, Morita S. BOIN-ET: Bayesian optimal interval design for dose finding based on both efficacy and toxicity outcomes. *Pharmaceutical Statistics* 2018; 17(4):383-395.

Yamaguchi Y, Takeda K, Yoshida S, Maruo K. Optimal biological dose selection in dose-finding trials with model-assisted designs based on efficacy and toxicity: a simulation study. *Journal of Biopharmaceutical Statistics* 2023; doi: 10.1080/10543406.2023.2202259.

Examples

```
n.dose      <- 6
start.dose  <- 1
size.cohort <- 3
n.cohort    <- 12

toxprob <- c(0.01,0.03,0.06,0.12,0.18,0.30)
effprob <- c(0.06,0.08,0.15,0.25,0.40,0.80)

phi   <- 0.33
delta <- 0.70

tau.T   <- 30
tau.E   <- 45
accrual <- 10

estpt.method <- "obs.prob"
obd.method   <- "max.effprob"
```

```
n.sim <- 10

boinet(
  n.dose=n.dose, start.dose=start.dose,
  size.cohort=size.cohort, n.cohort=n.cohort,
  toxprob=toxprob, effprob=effprob,
  phi=phi, delta=delta,
  tau.T=tau.T, tau.E=tau.E, accrual=accrual,
  estpt.method=estpt.method, obd.method=obd.method,
  n.sim=n.sim)
```

`fp.logit` *Fractional polynomial logistic regression*

Description

Fractional polynomial (FP) logistic regression with two degrees of freedom is performed to estimate the efficacy probabilities. The Best fitting FP model is chosen by not taking into account the closed testing procedure.

Usage

```
fp.logit(obs, n, dose)
```

Arguments

`obs`	Number of patients with events.
`n`	Number of patients.
`dose`	Dose levels to be investigated.

Value

The `fp.logit` returns a vector of estimated probabilities for each dose level.

`gboinet` *Conducting simulation study of gBOIN-ET design*

Description

Generalized Bayesian optimal interval design for optimal dose-finding accounting for ordinal graded efficacy and toxicity (gBOIN-ET design) is implemented under a scenario specified. 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.

Usage

```
gboinet(
  n.dose, start.dose, size.cohort, n.cohort,
  toxprob, effprob, sev.weight, res.weight,
  phi, phi1=phi*0.1, phi2=phi*1.4, delta, delta1=delta*0.6,
  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",
  stopping.npts=size.cohort*n.cohort,
  stopping.prob.T=0.95, stopping.prob.E=0.99,
  estpt.method, obd.method,
  w1=0.33, w2=1.09,
  plow.ast=phi1, pupp.ast=phi2, qlow.ast=delta1/2, qupp.ast=delta,
  psi00=40, psi11=60,
  n.sim=1000, seed.sim=100)
```

Arguments

n.dose	Number of dose.
start.dose	Starting dose. The lowest dose is generally recommended.
size.cohort	Cohort size.
n.cohort	Number of cohort.
toxprob	Vector of true toxicity probability.
effprob	Vector of true efficacy probability.
sev.weight	Vector of weight for toxicity category.
res.weight	Vector of weight for efficacy category.
phi	Target toxicity probability.
phi1	Highest toxicity probability that is deemed sub-therapeutic such that dose-escalation should be pursued. The default value is phi1=phi*0.1.
phi2	Lowest toxicity probability that is deemed overly toxic such that dose de-escalation is needed. The default value is phi2=phi*1.4.
delta	Target efficacy probability.
delta1	Minimum probability deemed efficacious such that the dose levels with less than delta1 are considered sub-therapeutic. The default value is delta1=delta*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 (days).
tau.E	Efficacy assessment windows (days).
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 (days) (average number of days necessary to enroll one patient).

`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"`.

`stopping.npts` Early study termination criteria for the number of patients. If the number of patients at the current dose reaches this criteria, the study is terminated. The default value is `stopping.npts=size.cohort*n.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 (`phi`) 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 (`delta1`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.E=0.99`.

`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=phi1`.

`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=phi2`.

`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=delta1/2`.

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=delta.
psi00	Score for toxicity=no and efficacy=no in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi00=40.
psi11	Score for toxicity=yes and efficacy=yes in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi11=60.
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 gboinet is a function which generates the operating characteristics of the generalized Bayesian optimal interval design for optimal dose-finding accounting for ordinal graded efficacy and toxicity (gBOIN-ET design) by a simulation study. Users can specify a variety of study settings to simulate studies, and choose methods to estimate the efficacy probability and to select the optimal biological dose. 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 gboinet returns a list containing the following components:

toxprob	True toxicity probability.
effprob	True efficacy probability.
nETS	Normalized equivalent toxicity score.
nEES	Normalized equivalent efficacy score.
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 (days).
tau.E	Efficacy assessment windows (days).
accrual	Accrual rate (days) (average number of days necessary to enroll one patient).
estpt.method	Method to estimate the efficacy probability.
obd.method	Method to select the optimal biological dose.
n.patient	Average number of patients who were treated at each dose level
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 and optimal biological dose was not selected.
duration	Expected study duration (days)

References

Takeda K, Morita S, Taguri M. gBOIN-ET: The generalized Bayesian optimal interval design for optimal dose-finding accounting for ordinal graded efficacy and toxicity in early clinical trials. *Biometrical Journal* 2022: 64(7):1178-1191.

Yamaguchi Y, Takeda K, Yoshida S, Maruo K. Optimal biological dose selection in dose-finding trials with model-assisted designs based on efficacy and toxicity: a simulation study. *Journal of Biopharmaceutical Statistics* 2023; doi: 10.1080/10543406.2023.2202259.

Examples

```
n.dose      <- 6
start.dose  <- 1
size.cohort <- 3
n.cohort    <- 12

toxprob <- rbind(c(0.94,0.87,0.79,0.68,0.62,0.50),
                 c(0.05,0.10,0.15,0.20,0.20,0.20),
                 c(0.01,0.03,0.05,0.10,0.15,0.25),
                 c(0.00,0.00,0.01,0.02,0.03,0.05))
effprob <- rbind(c(0.64,0.52,0.45,0.35,0.20,0.05),
                 c(0.30,0.40,0.40,0.40,0.40,0.15),
                 c(0.05,0.05,0.10,0.15,0.20,0.35),
                 c(0.01,0.03,0.05,0.10,0.20,0.45))

sev.weight <- c(0.00,0.50,1.00,1.50)
res.weight <- c(0.00,0.25,1.00,3.00)

phi   <- 0.33
delta <- 0.70

tau.T   <- 30
tau.E   <- 45
accrual <- 10

estpt.method <- "obs.prob"
obd.method   <- "max.effprob"

n.sim <- 10

gboinet(
  n.dose=n.dose, start.dose=start.dose,
  size.cohort=size.cohort, n.cohort=n.cohort,
  toxprob=toxprob, effprob=effprob,
  sev.weight=sev.weight, res.weight=res.weight,
  phi=phi, delta=delta,
  tau.T=tau.T, tau.E=tau.E, accrual=accrual,
  estpt.method=estpt.method, obd.method=obd.method,
  n.sim=n.sim)
```

`gridoptim` *Grid search to find optimal threshold values of toxicity and efficacy interval*

Description

Given non-informative prior probabilities of the six hypotheses, a grid search approach is used to find the optimal threshold values.

Usage

```
gridoptim(pi=rep(1/6,6), phi, phi1, phi2, delta, delta1, n=100)
```

Arguments

`pi`	Prior probability of 6 hypotheses. The default value is `pi=rep(1/6,6)`.
`phi`	Target toxicity probability.
`phi1`	Lower bound of toxicity probability.
`phi2`	Upper bound of toxicity probability.
`delta`	Target efficacy probability.
`delta1`	Lower bound of efficacy probability.
`n`	Number of patients. The default value is `n=100`.

Value

The `gridoptim` returns optimal threshold values of upper and lower toxicity/efficacy boundaries used in dose-escalation procedure.

Examples

```
gridoptim(phi=0.33,phi1=0.033,phi2=0.462,delta=0.70,delta1=0.42);
```

`multi.iso` *Model averaging of multiple unimodal isotopic regression*

Description

Given the location of the mode to be at each dose level, the unimodal isotonically transformed values are calculated. A frequentist model averaging approach is used to obtain the estimated efficacy probability.

Usage

```
multi.iso(obs, n)
```

Arguments

obs	Number of patients with events.
n	Number of patients.

Value

The multi.iso returns a vector of estimated probabilities for each dose level.

---

obd.select *Optimal biological dose selection*

Description

Optimal biological dose (OBD) is selected by a method specified.

Usage

```
obd.select(
  probt, probe, method,
  phi, phi1, phi2, delta, delta1,
  tterm, eterm, stopT, stopE,
  w1, w2,
  plow.ast, pupp.ast, qlow.ast, qupp.ast,
  psi00, psi11)
```

Arguments

probt	Estimated toxicity probability.
probe	Estimated efficacy probability.
method	Method used for OBD selection.
phi	Target toxicity probability.
phi1	Lower bound of toxicity probability.
phi2	Upper bound of toxicity probability.
delta	Target efficacy probability.
delta1	Lower bound of efficacy probability.
tterm	Probability of meeting toxicity stopping criteria.
eterm	Probability of meeting efficacy stopping criteria.
stopT	Toxicity stopping criteria.
stopE	Efficacy stopping criteria.
w1	Weight for toxicity-efficacy trade-off.
w2	Weight for penalty imposed on toxic doses.
plow.ast	Lower threshold of toxicity linear truncated function.

pupp.ast	Upper threshold of toxicity linear truncated function.
qlow.ast	Lower threshold of efficacy linear truncated function.
qupp.ast	Upper threshold of efficacy linear truncated function.
psi00	Score for toxicity=no and efficacy=no.
psi11	Score for toxicity=yes and efficacy=yes.

Value

The obd.select returns an optimal biological dose.

---

print.boinet *Print boinet*

Description

Display key summary results from boinet.

Usage

```
## S3 method for class 'boinet'
print(x, ...)
```

Arguments

x	Object from boinet.
...	More options to pass to print.

Value

No return values. Key summary results from boinet are displayed with trial design settings.

See Also

boinet

print.gboinet *Print gboinet*

Description

Display key summary results from gboinet.

Usage

```
## S3 method for class 'gboinet'
print(x, ...)
```

Arguments

x	Object from gboinet.
...	More options to pass to print.

Value

No return values. Key summary results from gboinet are displayed with trial design settings.

See Also

gboinet

print.tite.boinet *Print tite.boinet*

Description

Display key summary results from tite.boinet.

Usage

```
## S3 method for class 'tite.boinet'
print(x, ...)
```

Arguments

x	Object from tite.boinet.
...	More options to pass to print.

Value

No return values. Key summary results from tite.boinet are displayed with trial design settings.

See Also

tite.boinet

---

print.tite.gboinet *Print tite.gboinet*

Description

Display key summary results from tite.gboinet.

Usage

```
## S3 method for class 'tite.gboinet'
print(x, ...)
```

Arguments

x	Object from tite.gboinet.
...	More options to pass to print.

Value

No return values. Key summary results from tite.gboinet are displayed with trial design settings.

See Also

tite.gboinet

---

tite.boinet *Conducting simulation study of TITE-BOIN-ET design*

Description

Time-to-event Bayesian optimal interval design to accelerate dose-finding based on both efficacy and toxicity outcomes (TITE-BOIN-ET design) is implemented under a scenario specified. 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.

Usage

```
tite.boinet(
  n.dose, start.dose, size.cohort, n.cohort,
  toxprob, effprob,
  phi=0.3, phi1=phi*0.1, phi2=phi*1.4, delta=0.6, delta1=delta*0.6,
  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",
  stopping.npts=size.cohort*n.cohort,
  stopping.prob.T=0.95, stopping.prob.E=0.99,
  estpt.method, obd.method,
  w1= 0.33, w2=1.09,
  plow.ast=phi1, pupp.ast=phi2, qlow.ast=delta1/2, qupp.ast=delta,
  psi00=40, psi11=60,
  n.sim=1000, seed.sim=100)
```

Arguments

n.dose	Number of dose.
start.dose	Starting dose. The lowest dose is generally recommended.
size.cohort	Cohort size.
n.cohort	Number of cohort.
toxprob	Vector of true toxicity probability.
effprob	Vector of true efficacy probability.
phi	Target toxicity probability. The default value is phi=0.3.
phi1	Highest toxicity probability that is deemed sub-therapeutic such that dose-escalation should be pursued. The default value is phi1=phi*0.1.
phi2	Lowest toxicity probability that is deemed overly toxic such that dose de-escalation is needed. The default value is phi2=phi*1.4.
delta	Target efficacy probability. The default value is delta=0.6.
delta1	Minimum probability deemed efficacious such that the dose levels with less than delta1 are considered sub-therapeutic. The default value is delta1=delta*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 (days).
tau.E	Efficacy assessment windows (days).
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 (days) (average number of days necessary to enroll one patient).

`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"`.

`stopping.npts` Early study termination criteria for the number of patients. If the number of patients at the current dose reaches this criteria, the study is terminated. The default value is `stopping.npts=size.cohort*n.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 (`phi`) 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 (`delta1`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.E=0.99`.

`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=phi1`.

`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=phi2`.

`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=delta1/2`.

`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=delta`.

psi00	Score for toxicity=no and efficacy=no in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi00=40.
psi11	Score for toxicity=yes and efficacy=yes in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi11=60.
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 tite.boinet is a function which generates the operating characteristics of the time-to-event Bayesian optimal interval design to accelerate dose-finding based on both efficacy and toxicity outcomes (TITE-BOIN-ET design) by a simulation study. Users can specify a variety of study settings to simulate studies, and choose methods to estimate the efficacy probability and to select the optimal biological dose. 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 tite.boinet 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 (days).
tau.E	Efficacy assessment windows (days).
accrual	Accrual rate (days) (average number of days necessary to enroll one patient).
estpt.method	Method to estimate the efficacy probability.
obd.method	Method to select the optimal biological dose.
n.patient	Average number of patients who were treated at each dose level
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 and optimal biological dose was not selected.
duration	Expected study duration (days)

References

Takeda K, Morita S, Taguri M. TITE-BOIN-ET: Time-to-event Bayesian optimal interval design to accelerate dose-finding based on both efficacy and toxicity outcomes. *Pharmaceutical Statistics* 2020; 19(3):335-349.

Yamaguchi Y, Takeda K, Yoshida S, Maruo K. Optimal biological dose selection in dose-finding trials with model-assisted designs based on efficacy and toxicity: a simulation study. *Journal of Biopharmaceutical Statistics* 2023; doi: 10.1080/10543406.2023.2202259.

Examples

```
n.dose      <- 6
start.dose  <- 1
size.cohort <- 3
n.cohort    <- 12

toxprob <- c(0.01,0.03,0.06,0.12,0.18,0.30)
effprob <- c(0.06,0.08,0.15,0.25,0.40,0.80)

phi   <- 0.33
delta <- 0.70

tau.T   <- 30
tau.E   <- 45
accrual <- 10

estpt.method <- "obs.prob"
obd.method   <- "max.effprob"

n.sim <- 10

tite.boinet(
  n.dose=n.dose, start.dose=start.dose,
  size.cohort=size.cohort, n.cohort=n.cohort,
  toxprob=toxprob, effprob=effprob,
  phi=phi, delta=delta,
  tau.T=tau.T, tau.E=tau.E, accrual=accrual,
  estpt.method=estpt.method, obd.method=obd.method,
  n.sim=n.sim)
```

---

tite.gboinet *Conducting simulation study of TITE-gBOIN-ET design*

Description

Time-to-event generalized Bayesian optimal interval design to accelerate dose-finding accounting for ordinal graded efficacy and toxicity outcomes (TITE-gBOIN-ET design) is implemented under a scenario specified. 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.

Usage

```
tite.gboinet(
  n.dose, start.dose, size.cohort, n.cohort,
  toxprob, effprob, sev.weight, res.weight,
  phi, phi1=phi*0.1, phi2=phi*1.4, delta, delta1=delta*0.6,
  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",
  stopping.npts=size.cohort*n.cohort,
  stopping.prob.T=0.95, stopping.prob.E=0.99,
  estpt.method, obd.method,
  w1=0.33, w2=1.09,
  plow.ast=phi1, pupp.ast=phi2, qlow.ast=delta1/2, qupp.ast=delta,
  psi00=40, psi11=60,
  n.sim=1000, seed.sim=100)
```

Arguments

n.dose	Number of dose.
start.dose	Starting dose. The lowest dose is generally recommended.
size.cohort	Cohort size.
n.cohort	Number of cohort.
toxprob	Vector of true toxicity probability.
effprob	Vector of true efficacy probability.
sev.weight	Vector of weight for toxicity category.
res.weight	Vector of weight for efficacy category.
phi	Target toxicity probability.
phi1	Highest toxicity probability that is deemed sub-therapeutic such that dose-escalation should be pursued. The default value is phi1=phi*0.1.
phi2	Lowest toxicity probability that is deemed overly toxic such that dose de-escalation is needed. The default value is phi2=phi*1.4.
delta	Target efficacy probability.
delta1	Minimum probability deemed efficacious such that the dose levels with less than delta1 are considered sub-therapeutic. The default value is delta1=delta*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 (days).
tau.E	Efficacy assessment windows (days).
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 (days) (average number of days necessary to enroll one patient).

`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"`.

`stopping.npts` Early study termination criteria for the number of patients. If the number of patients at the current dose reaches this criteria, the study is terminated. The default value is `stopping.npts=size.cohort*n.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 (`phi`) 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 (`delta1`) is larger than this criteria, the dose levels are eliminated from the study. The default value is `stopping.prob.E=0.99`.

`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=phi1`.

`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=phi2`.

`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=delta1/2`.

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=delta.
psi00	Score for toxicity=no and efficacy=no in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi00=40.
psi11	Score for toxicity=yes and efficacy=yes in utility defined by scoring. This must be specified when using obd.method="utility.scoring". The default value is psi11=60.
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 tite.gboinet is a function which generates the operating characteristics of the time-to-event generalized Bayesian optimal interval design to accelerate dose-finding accounting for ordinal graded efficacy and toxicity outcomes (TITE-gBOIN-ET design) by a simulation study. Users can specify a variety of study settings to simulate studies, and choose methods to estimate the efficacy probability and to select the optimal biological dose. 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 tite.gboinet returns a list containing the following components:

toxprob	True toxicity probability.
effprob	True efficacy probability.
nETS	Normalized equivalent toxicity score.
nEES	Normalized equivalent efficacy score.
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 (days).
tau.E	Efficacy assessment windows (days).
accrual	Accrual rate (days) (average number of days necessary to enroll one patient).
estpt.method	Method to estimate the efficacy probability.
obd.method	Method to select the optimal biological dose.
n.patient	Average number of patients who were treated at each dose level
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 and optimal biological dose was not selected.
duration	Expected study duration (days)

References

Takeda K, Yamaguchi Y, Taguri M, Morita S. TITE-gBOIN-ET: Time-to-event generalized Bayesian optimal interval design to accelerate dose-finding accounting for ordinal graded efficacy and toxicity outcomes. *Biometrical Journal* 2023 (in press).

Yamaguchi Y, Takeda K, Yoshida S, Maruo K. Optimal biological dose selection in dose-finding trials with model-assisted designs based on efficacy and toxicity: a simulation study. *Journal of Biopharmaceutical Statistics* 2023; doi: 10.1080/10543406.2023.2202259.

Examples

```
n.dose      <- 6
start.dose  <- 1
size.cohort <- 3
n.cohort    <- 12

toxprob <- rbind(c(0.94,0.87,0.79,0.68,0.62,0.50),
                 c(0.05,0.10,0.15,0.20,0.20,0.20),
                 c(0.01,0.03,0.05,0.10,0.15,0.25),
                 c(0.00,0.00,0.01,0.02,0.03,0.05))
effprob <- rbind(c(0.64,0.52,0.45,0.35,0.20,0.05),
                 c(0.30,0.40,0.40,0.40,0.40,0.15),
                 c(0.05,0.05,0.10,0.15,0.20,0.35),
                 c(0.01,0.03,0.05,0.10,0.20,0.45))

sev.weight <- c(0.00,0.50,1.00,1.50)
res.weight <- c(0.00,0.25,1.00,3.00)

phi   <- 0.33
delta <- 0.70

tau.T   <- 30
tau.E   <- 45
accrual <- 10

estpt.method <- "obs.prob"
obd.method   <- "max.effprob"

n.sim <- 10

tite.gboinet(
  n.dose=n.dose, start.dose=start.dose,
  size.cohort=size.cohort, n.cohort=n.cohort,
  toxprob=toxprob, effprob=effprob,
  sev.weight=sev.weight, res.weight=res.weight,
  phi=phi, delta=delta,
  tau.T=tau.T, tau.E=tau.E, accrual=accrual,
  estpt.method=estpt.method, obd.method=obd.method,
  n.sim=n.sim)
```

utility.scoring *Utility defined by scoring*

Description

Given estimated toxicity and efficacy probabilities, the utility which is defined by scoring is calculated.

Usage

```
utility.scoring(probt, probe, psi00, psi11)
```

Arguments

probt	Estimated toxicity probability.
probe	Estimated efficacy probability.
psi00	Score for toxicity=no and efficacy=no.
psi11	Score for toxicity=yes and efficacy=yes.

Value

The utility.scoring returns a utility value defined by the scoring.

utility.truncated.linear *Utility defined by truncated linear function*

Description

Given estimated toxicity and efficacy probabilities, the utility which is defined by truncated linear functions is Calculated.

Usage

```
utility.truncated.linear(probt, probe, tlow, tupp, elow, eupp)
```

Arguments

probt	Estimated toxicity probability
probe	Estimated efficacy probability
tlow	Lower threshold of toxicity linear truncated function.
tupp	Upper threshold of toxicity linear truncated function.
elow	Lower threshold of efficacy linear truncated function.
eupp	Upper threshold of efficacy linear truncated function.

Value

The `utility.truncated.linear` returns a utility value defined by the truncated linear functions.

`utility.weighted` *Utility defined by weighted function*

Description

Given estimated toxicity and efficacy probabilities, the utility which is defined by a weighted function is Calculated.

Usage

```
utility.weighted(probt, probe, w1, w2, tox.upper)
```

Arguments

`probt`	Estimated toxicity probability.
`probe`	Estimated efficacy probability.
`w1`	Weight for toxicity-efficacy trade-off.
`w2`	Weight for penalty imposed on toxic doses.
`tox.upper`	Upper bound of toxicity probability.

Value

The `utility.weighted` returns a utility value defined by the weighted function.

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