Package 'BOIN'

September 19, 2014

Type Package

Title Bayesian Optimal Interval Design for Phase I Clinical Trials

Version 1.0

Date 2014-08-14

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Description The Bayesian optimal interval (BOIN) design is a novel phase I clinical trial design for finding the maximum tolerated dose (MTD). The BOIN design is motivated by the top priority and concern of clinicians when testing a new drug, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses. The prominent advantage of the BOIN design is that it achieves simplicity and superior performance at the same time. The BOIN design is algorithm-based and can be implemented in a simple way similar to the traditional 3+3 design. The BOIN design yields average performance comparable to the continual reassessment method (CRM, one of the best model-based design) in terms of selecting the MTD, but has a substantially lower risk of assigning patients to subtherapeutic or overly toxic doses.

License GPL-2

NeedsCompilation no

Repository CRAN

Date/Publication 2014-09-19 17:28:46

R topics documented:

BOIN-package *Bayesian Optimum Interval (BOIN) design for finding the maximum tolerated dose (MTD)*

Description

Package is used to design phase I clinical trials using the BOIN design. The BOIN design is motivated by top priority and concern of clinicians, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses. The prominent advantage of the BOIN design is that it achieves simplicity and superior performance at the same time. The BOIN design is algorithm-based and can be implemented in a simple way similar to the traditional "3+3" design. The BOIN design yields average performance comparable to the continual reassessment method (CRM, one of the best model-based designs) in terms of selecting the MTD, but has a substantially lower risk of assigning patients to subtherapeutic or overly toxic doses.

Details

Package:	BOIN
Type:	Package
Version:	1.0
Date:	2014-06-05
License:	GPL-2

Author(s)

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References

Liu S. and Yuan, Y. (2014). Bayesian Optimal Interval Designs for Phase I Clinical Trials, *Journal of the Royal Statistical Society: Series C*, to appear

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software_release/OptInterval/tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software_release/OptInterval/paper.pdf

Examples

```
###### Trial Design #####
get.boundary(target=0.3, ncohort=10, cohortsize=3)
```

```
###### Obtain operating characteristics #####
get.oc(target=0.3, p.true=c(0.05, 0.15, 0.3, 0.45, 0.6), ncohort=10, cohortsize=3, ntrial=1000)

##### Select the MTD when the trial is completed #####
n<-c(3, 3, 15, 9, 0)
y<-c(0, 0, 4, 4, 0)
select.mtd(target=0.3, ntox=y, npts=n)
```

`get.boundary` *Generate dose escalation and deescalation boundaries*

Description

Generate the optimal dose escalation and deescalation boundaries for conducting the trial.

Usage

```
get.boundary(target, ncohort, cohortsize = 3, p.saf = "default", p.tox = "default",
design = 1, cutoff.eli = 0.95, extrasafe = FALSE, offset = 0.05, print = TRUE)
```

Arguments

`target`	target toxicity rate
`ncohort`	the total number of cohort
`cohortsize`	the cohort size
`p.saf`	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be made.The default value is `p.saf=0.6xtarget`.
`p.tox`	the loweset toxicity probability that is deemed overly toxic such that deescalation is required. The default value is `p.tox=1.4xtarget`.
`design`	to use the local optimal design (the default, `design=1`) or the global optimal design (`design=2`). We generally recommend the local optimal design.
`cutoff.eli`	the cutoff to eliminate the 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 strict stopping rule for extra safety
`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.
`print`	prints out the boundary results.

Details

The dose escalation and deescalation boundaries are all we need to run a phase I trial when using the BOIN design. The decision of which dose to administer to the next cohort of patients does not require complicated computations, but only a simple comparison of the observed toxicity rate at the current dose with the dose escalation and deescalation boundaries. If the observed toxicity rate at the current dose is smaller than or equal to the escalation boundary, we escalate the dose; if the observed toxicity rate at the current dose is greater than or equal to the deescalation boundary, we deescalate the dose; otherwise, we retain the current dose. The dose escalation and deescalation boundaries are chosen to minimize the probability of assigning patients to subtherapeutic or overly toxic doses, thereby optimizing patient ethics.

`get.boundary` also outputs elimination boundary, which is used to prevent treating patients at overly toxic doses based on the following Bayesian safety rule:

if $pr(p_j > \phi | m_j, n_j) > 0.95$ and $n_j \geq 3$, dose levels *j* and higher are eliminated from the trial,

where p_j is the toxicity probability of dose level *j*, ϕ is the target toxicity rate, m_j and n_j are the number of toxicities and patients treated at dose level *j*. The trial is terminated if the lowest dose is eliminated.

The BOIN design has a built-in stopping rule, i.e., stop the trial if the lowest dose is eliminated due to toxicity. For some applications, investigators may prefer a more strict stopping rule for extra safety when the lowest dose is overly toxic. Setting `extrasafe=TRUE` imposes the following more strict stopping rule: stop the trial if (1) the number of patients treated at the lowest dose >=3, and (2) Pr(toxicity rate of the lowest dose > `target` | data) > `cutoff.eli-offset`. As a tradeoff, the strong stopping rule will decrease the selection percentage of the MTD when the lowest dose actually is the MTD.

Value

`get.boundary` returns the optimal dose escalation and deescalation boundaries for running the trial. The dose elimination boundary is also returned for preventing continuously exposing patients to overly toxic doses.

Note

We recommend to use the local BOIN design (i.e., the default option) because of its better operating characteristics and simplicity. We should avoid setting the values of `p.saf` and `p.tox` very close to `target`. This is because the small sample sizes of typical phase I trials prevent us from differentiating the target toxicity rate from the rates close to it. In addition, in most clinical applications, the target toxicity rate is often a rough guess, and finding a dose level with a toxicity rate reasonably close to the target rate will still prove to be of interest to the investigator. The default values provided by `get.boundary` are generally reasonable for most clinical applications.

Author(s)

Suyu Liu and Ying Yuan (yyuan@mdanderson.org)

References

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See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software_release/OptInterval/tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software_release/OptInterval/paper.pdf

Examples

```
## Consider a phase I trial aiming to find the MTD with a target toxicity rate of 0.3
## the maximum sample size is 30 patients in cohort size of 3

get.boundary(target=0.3, ncohort=10, cohortsize=3)
```

`get.oc` *Generate operating characteristics*

Description

Obtain the operating characteristics of the BOIN design by simulating trials.

Usage

```
get.oc(target, p.true, ncohort, cohortsize, startdose = 1, p.saf = "default",
p.tox = "default",  design = 1, cutoff.eli = 0.95, extrasafe = FALSE,
offset = 0.05, ntrial = 1000)
```

Arguments

`target`	target toxicity rate
`p.true`	a vector containing the true toxicity probabilities of the investigational dose levels.
`ncohort`	the total number of cohorts
`cohortsize`	the cohort size
`startdose`	the starting dose level for the trial
`p.saf`	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be made.The default value is `p.saf=0.6xtarget`.
`p.tox`	the loweset toxicity probability that is deemed overly toxic such that deescalation is required. The default value is `p.tox=1.4xtarget`.
`design`	to use the local optimal design (the default, `design=1`) or the global optimal design (`design=2`).
`cutoff.eli`	the cutoff to eliminate the 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
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.
ntrial	the total number of trials to be simulated.

Details

The operating characteristics of the BOIN design are generated by simulating trials under the pre-specified true toxicity probabilities of the investigational doses. The BOIN design has a built-in stopping rule, i.e., stop the trial if the lowest dose is eliminated due to toxicity. For some applications, investigators may prefer a more strict stopping rule for extra safety when the lowest dose is overly toxic. Setting extrasafe=TRUE imposes the following more strict stopping rule: stop the trial if (1) the number of patients treated at the lowest dose >=3, and (2) Pr(toxicity rate of the lowest dose > target | data) > cutoff.eli-offset. As a tradeoff, the strong stopping rule will decrease the selection percentage of the MTD when the lowest dose actually is the MTD.

Value

get.oc returns the operating characteristics of the BOIN design, including (1) selection percentage at each dose level, (2) the number of patients treated at each dose level, (3) the number of toxicity observed at each dose level, (4) the average number of toxicities, (5) the average number of patients, (6) the risk of poor allocation and (7) the risk of toxicity.

Note

We recommend to use the local BOIN design (i.e., the default option) because of its better operating characteristics and simplicity. We should avoid setting the values of p.saf and p.tox very close to target. This is because the small sample sizes of typical phase I trials prevent us from differentiating the target toxicity rate from the rates close to it. In addition, in most clinical applications, the target toxicity rate is often a rough guess, and finding a dose level with a toxicity rate reasonably close to the target rate will still prove to be of interest to the investigator. The default values provided by get.boundary are generally reasonable for most clinical applications.

Author(s)

Suyu Liu and Ying Yuan (yyuan@mdanderson.org)

References

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Examples

```
## Consider a phase I trial aiming to find the MTD with a target toxicity rate of 0.3
## the maximum sample size is 30 patients in cohort size of 3
## assume the true toxicity rates of 5 doses are (0.05, 0.15, 0.3, 0.45, 0.6)
## run 1,000 simulated trials
ptox = c(0.05, 0.15, 0.3, 0.45, 0.6)
get.oc(target=0.3, p.true=ptox, ncohort=10, cohortsize=3, ntrial=1000)
```

`select.mtd` *Select the maximum tolerated dose (MTD)*

Description

`select.mtd` is used to select the maximum tolerated dose (MTD) when the trial is completed.

Usage

```
select.mtd(target, ntox, npts, cutoff.eli = 0.95, print=TRUE)
```

Arguments

`target`	target toxicity rate
`ntox`	a vector containing the number of patients experienced dose-limiting toxicity at each dose level
`npts`	a vector containing the number of patients treated at each dose level
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of (`cutoff.eli=0.95`) for general use.
`print`	prints out the dose selection result.

Details

`select.mtd` selects the MTD based on isotonic estimates of toxicity probabilities. `select.mtd` selects as the MTD dose j^*, for which the isotonic estimate of toxicity rate is closet to the `target`. If there are ties, we select from ties the highest dose level when the estimate of toxicity rate is smaller than `target`, or the lowest dose level when the estimate of toxicity rate is greater than `target`. The isotonic estimates are obtained by the pooled-adjacent-violators algorithm (PAVA) (Barlow, 1972).

Value

`select.mtd` returns the MTD based on the trial data.

Note

The MTD selection and dose escalation/deescalation rule are two independent components of the trial design. When appropriate, other dose selection procedure (e.g., based on a fitted logistic model) can also be used to select the MTD after the completion of the trial using the BOIN design.

Author(s)

Suyu Liu and Ying Yuan (yyuan@mdanderson.org)

References

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See Also

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Paper: http://odin.mdacc.tmc.edu/~yyuan/Software_release/OptInterval/paper.pdf

Examples

```
##### Select the MTD based on the trial data #####
n<-c(3, 3, 15, 9, 0)    #the number of patients treated at 5 investigational doses
y<-c(0, 0, 4, 4, 0)     #the number of patients experienced toxicity at 5 doses
select.mtd(target=0.3, ntox=y, npts=n)
```

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