Package ‘BOIN’

September 4, 2015

Type Package
Description The Bayesian optimal interval (BOIN) design is a novel phase I clinical trial design for finding the maximum tolerated dose (MTD). It can be used to design both single-agent and drug-combination trials. 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 an average performance that is comparable to that of 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.

License GPL-2

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Description

The package is used to design single-agent or drug-combination phase I clinical trials using the BOIN design. The BOIN design is motivated by the 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 a 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 an average performance that is comparable to that of 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: 2.0
Date: 2015-08-20
License: GPL-2

Author(s)

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References


See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf
Examples

# Example 1. Single-agent Phase I Trial#

# 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)

# Obtain dose escalation boundaries for trial conduct
get.boundary(target=0.3, ncohort=10, cohortsize=3)

# 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, npts=n, ntox=y)

# Example 2. A 3x5 Drug-combination Phase I Trial#

# Obtain operating characteristics
p.true = matrix(c(0.05, 0.10, 0.15, 0.30, 0.45, 0.10, 0.15, 0.30, 0.45, 0.55, 0.15, 0.30, 0.45, 0.50, 0.60), ncol=5, byrow=TRUE)
get.oc.comb(target=0.3, p.true, ncohort=40, cohortsize=1, ntrial=1000)

# Obtain dose escalation boundaries for trial conduct
get.boundary(target=0.3, ncohort=40, cohortsize=1)

# Make the decision of dose escalation/deescalation during the course of trial conduct
# matrix n contains the number of patients treated at each dose combination
# matrix y contains the number of patients experienced toxicity at each dose combination
n<-matrix(c(3, 0, 0, 0, 0, 7, 6, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0), ncol=5, byrow=TRUE)
y<-matrix(c(0, 0, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0), ncol=5, byrow=TRUE)
conduct.comb(target=0.3, npts=n, ntox=y, dose.curr=c(2, 2))

# Select the MTD when the combination trial is completed
n<-matrix(c(3, 5, 0, 0, 0, 7, 6, 15, 0, 0, 0, 0, 4, 0, 0), ncol=5, byrow=TRUE)
y<-matrix(c(0, 1, 0, 0, 0, 1, 1, 4, 0, 0, 0, 0, 2, 0, 0), ncol=5, byrow=TRUE)
select.mtd.comb(target=0.3, npts=n, ntox=y)

---

**Description**

Determine the dose for the next cohort of new patients during the trial conduct for drug combination trials.
Usage

```
conduct.comb(target, npts, ntox, dose.curr, n.earlystop=100, p.saf="default", p.tox="default", cutoff.eli=0.95, extrasafe=FALSE, offset=0.05)
```

Arguments

- **target**: target toxicity rate
- **npts**: a matrix containing the number of patients treated at each dose combination
- **ntox**: a matrix containing the number of patients who experienced dose-limiting toxicities at each dose combination
- **dose.curr**: the current dose combination
- **n.earlystop**: Early stopping parameter. If the number of patients treated at the current dose reaches `n.earlystop`, stop the trial and select the MTD based on the observed data. The default value `n.earlystop=100` essentially turns off this type of early stopping.
- **p.saf**: the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that dose escalation should be undertaken. The default value is `p.saf=0.6 \times target`.
- **p.tox**: the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is `p.tox=1.4 \times target`.
- **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
- **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.

Details

This function is used for conducting combination trials. Given the currently observed data, `conduct.comb()` determines dose combination for treating the next cohort of new patients. The currently observed data include: the number of patients treated at each dose combination (i.e., `npts`), the number of patients who experienced dose-limiting toxicities at each dose combination (i.e., `ntox`), and the level of current dose (i.e., `dose`).

Value

`conduct.comb()` returns the dose for treating the next cohort of new patients.

Author(s)

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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, n.earlystop = 100,
p.saf = "default", p.tox = "default", cutoff.eli = 0.95,
extrasafe = FALSE, offset = 0.05, print = TRUE)

Arguments

target  target toxicity rate
ncohort the total number of cohorts
cohortsize the cohort size
n.earlystop Early stopping parameter. If the number of patients treated at the current dose reaches n.earlystop, stop the trial and select the MTD based on the observed data. The default value n.earlystop=100 essentially turns off the type of early stopping.

References


See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf

Examples

```r
# Consider a 3x5 drug combination phase I trial aiming to find the MTD with
# a target toxicity rate of 0.3. Assume that the current dose is (2, 2),
# matrix n contains the number of patients treated at each combinations,
# and matrix y the number of patients experienced dose-limiting toxicity
# at each combinations.

n<-matrix(c(3, 0, 0, 0, 0, 7, 6, 0, 0, 0, 0, 0, 0, 0, 0, 0), ncol=5, byrow=TRUE)
y<-matrix(c(0, 0, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0), ncol=5, byrow=TRUE)
conduct.comb(target=0.3, npts=n, ntox=y, dose.curr=c(2, 2))
```
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 the elimination boundary, which is used to avoid 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 \( j \), \( \phi \) is the target toxicity rate, and \( m_j \) 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 two built-in stopping rules: (1) stop the trial if the lowest dose is eliminated due to toxicity, and no dose should be selected as the MTD; and (2) stop the trial and select the MTD if the number of patients treated at the current dose reaches \( n \_earlystop \). The first stopping rule is a safety rule to protect patients from the case in which all doses are overly toxic. The rationale for the second stopping rule is that when there is a large number (i.e., \( n \_earlystop \)) of patients assigned to a dose, it means that the dose-finding algorithm has approximately converged. Thus, we can stop the trial early and select the MTD to save the sample size and reduce the trial duration.

For some applications, investigators may prefer a more strict safety stopping rule than rule (1) for extra safety when the lowest dose is overly toxic. This can be achieved by setting extrasafe=TRUE, which imposes the following more strict safety stopping rule: stop the trial if (i) the number of patients treated at the lowest dose \( \geq 3 \), and (ii) \( Pr \) (toxicity rate of the lowest dose > target | data) > cutoff.eli-offset. As a tradeoff, the strong stopping rule will decrease the MTD selection percentage when the lowest dose actually is the MTD.
Value

`getboundary()` returns the optimal dose escalation and deescalation boundaries for running the trial. The dose elimination boundary is also returned for preventing the continuous exposure of patients to overly toxic doses.

Note

We should avoid setting the values of `p_saf` and `p_tox` very close to the 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 be of interest to the investigator. The default values provided by `getboundary()` are generally reasonable for most clinical applications.

Author(s)

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

References


See Also

Tutorial: [http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf](http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf)


Examples

```r
## 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

getboundary(target=0.3, ncohort=10, cohortsize=3)
```

---

`get.oc` **Generate operating characteristics for single agent trials**

Description

Obtain the operating characteristics of the BOIN design for single agent trials by simulating trials.
Usage

get.oc(target, p.true, ncohort, cohortsize, n.earlystop=100, startdose=1, p.saf="default", p.tox="default", 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

n.earlystop Early stopping parameter. If the number of patients treated at the current dose reaches n.earlystop, stop the trial and select the MTD based on the observed data. The default value n.earlystop=100 essentially turns off this type of early stopping.

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 undertaken. The default value is p.saf=0.6 \times target.

p.tox the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4 \times target.

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

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 two built-in stopping rules: (1) stop the trial if the lowest dose is eliminated due to toxicity, and no dose should be selected as the MTD; and (2) stop the trial and select the MTD if the number of patients treated at the current dose reaches n.earlystop. The first stopping rule is a safety rule to protect patients from the case in which all doses are overly toxic. The rationale for the second stopping rule is that when there is a large number (i.e., n.earlystop) of patients assigned to a dose, it means that the dose-finding algorithm has approximately converged. Thus, we can stop the trial early and select the MTD to save sample size and reduce the trial duration.

For some applications, investigators may prefer a more strict safety stopping rule than rule (1) for extra safety when the lowest dose is overly toxic. This can be achieved by setting extrasafe=TRUE, which imposes the following more strict safety stopping rule: stop the trial if (i) the number of patients treated at the lowest dose >=3, and (ii) Pr(toxicity rate of the lowest dose > target | data)
get.oc

> cutoff.eli-offset. As a tradeoff, the strong stopping rule will decrease the MTD selection percentage when the lowest dose actually is the MTD.

Value

get.oc() returns the operating characteristics of the BOIN design as a data frame, including (1) function arguments (1) selection percentage at each dose level (selpercent), (2) the number of patients treated at each dose level (nptsdose), (3) the number of toxicities observed at each dose level (ntoxdose), (4) the average number of toxicities (totaltox), (5) the average number of patients (totaln), and (6) the percentage of early stopping without selecting the MTD (pctearlystop).

Note

We should avoid setting the values of \( p_{\text{saf}} \) and \( p_{\text{tox}} \) very close to the 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 be of interest to the investigator. The default values provided by get.oc() are generally reasonable for most clinical applications.

Author(s)

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

References


See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf


Examples

```r
## Consider a phase I trial aiming to find the MTD with a target toxicity rate of 0.3
## the maximum sample size is 25 patients in cohort size of 1
## 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=25, cohortsize=1, ntrial=1000)
```
Description

Obtain the operating characteristics of the BOIN design for drug combination trials

Usage

get.oc.comb(target, p.true, ncohort, cohortsize, n.earlystop=100, startdose=c(1, 1), p.saf="default", p.tox="default", cutoff.eli=0.95, extrasafe=FALSE, offset=0.05, ntrial=1000)

Arguments

target target toxicity rate
p.true a JxK matrix containing the true toxicity probabilities of combinations with J dose levels of agent A and K dose levels of agent B.
ncohort the total number of cohorts
cohortsize the cohort size
n.earlystop Early stopping parameter. If the number of patients treated at the current dose reaches n.earlystop, stop the trial and select the MTD based on the observed data. The default value n.earlystop=100 essentially turns off this type of early stopping.
startdose the starting dose combination 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 undertaken. The default value is p.saf=0.6 x target.
p.tox the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4 x target.
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
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 two built-in stopping rules: (1) stop the trial if the lowest dose is eliminated due to toxicity, and no dose should be selected as the MTD; and (2) stop the trial and select the MTD if the number of patients treated
at the current dose reaches \( n.\text{earlystop} \). The first stopping rule is a safety rule to protect patients from the case in which all doses are overly toxic. The rationale for the second stopping rule is that when there is a large number (i.e., \( n.\text{earlystop} \)) of patients assigned to a dose, it means that the dose-finding algorithm has approximately converged. Thus, we can stop the trial early and select the MTD to save sample size and reduce the trial duration.

For some applications, investigators may prefer a more strict safety stopping rule than rule (1) for extra safety when the lowest dose is overly toxic. This can be achieved by setting \texttt{extrasafe=TRUE}, which imposes the following more strict safety stopping rule: stop the trial if (i) the number of patients treated at the lowest dose >=3, and (ii) \( \Pr(\text{toxicity rate of the lowest dose} > \text{target I data}) > \text{cutoff.eli-offset} \). As a tradeoff, the strong stopping rule will decrease the MTD selection percentage when the lowest dose actually is the MTD.

**Value**

\texttt{get.oc.comb()} returns the operating characteristics of the BOIN design as a list, including (1) selection percentage at each dose level (\texttt{selpercent}), (2) the number of patients treated at each dose level (\texttt{nptsdose}), (3) the number of toxicities observed at each dose level (\texttt{ntoxdose}), (4) the total correct selection of the MTD (\texttt{mtdpercent}), (5) the total percentage of patients treated at the MTD (\texttt{mtdpts}).

**Note**

We should avoid setting the values of \texttt{p.saf} and \texttt{p.tox} very close to the \texttt{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 be of interest to the investigator. The default values provided by \texttt{get.oc.comb()} are generally reasonable for most clinical applications.

**Author(s)**

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

**References**


**See Also**

Tutorial: [http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf](http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf)

Examples

```r
## Consider a 3x5 drug combination trial with 3 doses of agent A and
## 5 doses of agent B. The goal is to find the MTD with a target toxicity
## rate of 0.3 with the maximum sample size of 40 patients in cohort size
## of 1. A total of 1,000 trials are simulated. p.true is a 3x5 matrix
## containing the true toxicity probabilities of dose combinations

p.true = matrix(c(0.05, 0.10, 0.15, 0.30, 0.45, 0.10, 0.15, 0.30, 0.45, 0.55,
                  0.15, 0.30, 0.45, 0.50, 0.60), ncol=5, byrow=TRUE)
get.oc.comb(target=0.3, p.true, ncohort=40, cohortsize=1, ntrial=1000)
```

Description

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

Usage

```r
select.mtd(target, npts, ntox, cutoff.eli=0.95, extrasafe=False, offset=0.05, print=TRUE)
```

Arguments

- `target`: target toxicity rate
- `npts`: a vector containing the number of patients treated at each dose level
- `ntox`: a vector containing the number of patients who experienced dose-limiting toxicity 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.
- `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 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 the toxicity rate is closest to the target. If there are ties, we select from the ties the highest dose level when the estimate of the toxicity rate is smaller than the target, or the lowest dose level when the estimate of the toxicity rate is greater than the 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, another dose selection procedure (e.g., based on a fitted logistic model) can 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


See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf


Examples

```r
## 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, n.tox = y, n.pets = n)
```

```
select.mtd.comb

Select the maximum tolerated dose (MTD) for drug combination trials
```

Description

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

Usage

```r
select.mtd.comb(target, n.pets, n.tox, cutoff.eli = 0.95, extrasafe = FALSE, offset = 0.05, print = TRUE)
```
Arguments

- **target**: target toxicity rate
- **npts**: a matrix containing the number of patients treated at each dose combination
- **ntox**: a matrix containing the number of patients experienced dose-limiting toxicity at each dose combination
- **cutoff.eli**: the cutoff to eliminate overly toxic doses 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 dose selection result.

Details

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

Value

`select.mtd.comb()` 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, another dose selection procedure (e.g., based on a fitted logistic model) can 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


See Also

- Tutorial: [http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf](http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.0_tutorial.pdf)
Examples

```r
## Select the MTD based on the data from a 3x5 combination trial
## matrix n contains the number of patients treated at each dose combination
## matrix y contains the number of patients experienced toxicity at each dose combination

n <- matrix(c(3, 5, 0, 0, 7, 6, 15, 0, 0, 0, 4, 0, 0), ncol=5, byrow=TRUE)
y <- matrix(c(0, 1, 0, 0, 1, 1, 4, 0, 0, 0, 2, 0, 0), ncol=5, byrow=TRUE)
select.mtd.comb(target=0.3, npts=n, ntox=y)
```
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