Package 'TEQR'

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Title Target Equivalence Range Design

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Depends

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Description The TEQR package contains software to calculate the operating characteristics for the TEQR and the ACT designs.The TEQR (toxicity equivalence range) design is a toxicity based cumulative cohort design with added safety rules. The ACT (Activity constrained for toxicity) design is also a cumulative cohort design with additional safety rules. The unique feature of this design is that dose is escalated based on lack of activity rather than on lack of toxicity and is de-escalated only if an unacceptable level of toxicity is experienced.

License GPL-2

NeedsCompilation no

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R topics documented:

Description

desc caculates select descriptive statistics for the variable y.

Usage

```
desc(y, pcts=c(0.025,0.05,0.95,0.975), nsig=4)
```

Arguments

y	variable of interest
pcts	selected percentiles, the default is c(0.025,0.05,0.95,0.975)
nsig	number of significant figures

Value

desc prints descriptive statistics including mean, median, standard deviation,range, min, max and selected percentiles.

Author(s)

M.S. Blanchard <sblanchard@coh.org>

Examples

```
set.seed(1111)
OperChar<-teqrOCtox(
sim=500,
firstdose=2,
probt=c(.05,.15,.23,.34,.51,.76),
cohortSize=3,
MaxNoCohorts=30,
MTDss=12,
pTarget=.2,
eq1=.05,
eq2=.05,
tootoxic=.34)
OperChar
TotalN<-rep(NA,500)
for (i in 1:500){
TotalN[i]<-sum(OperChar$DLdata$dllength[OperChar$DLdata$simNo==i])
}
desc(TotalN)
```

---

print.teqrDG *print.teqrDG*

Description

Print file for the class teqrDG.

Usage

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

Arguments

x   object of class teqrDG

...   additional arguments to be passed to lower level functions

Value

The output from print.teqrDG is the dose escalation/expansion/de-escalation guidelines table.

Author(s)

M.S. Blanchard <sblanchard@coh.org>

Examples

```
output<-teqrDG(TotalN=12,pTarget=0.2,eq1=0.05,eq2=0.05,tootoxic=0.34)
output
```

---

print.teqrOCact *print.teqrOCact*

Description

Print file for the class teqrOCact.

Usage

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

Arguments

x   object of class teqrOCact

...   additional arguments to be passed to lower level functions

Value

The output from print.teqr is a listing of the operating characteristics for the design as specified by the user.

Author(s)

M.S. Blanchard <sblanchard@coh.org>

Examples

```
set.seed(1111)
OperChar<-teqrOCact(
sim=1000,
firstdose=2,
proba=c(0.50,0.80,0.90),
probc=c(0.10,0.10,0.10),
cohortSize=3,
MaxNoCohorts=30,
RP2Dss=6,
pTarget=1.00,
eq1=0.34,
eq2=0.0,
toxcon=0.34,
llactivity=0.66)
OperChar
```

---

print.teqrOCtox   *print.teqrOCtox*

Description

Print file for the class teqrOCtox.

Usage

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

Arguments

x	object of class teqrOCtox
...	additional arguments to be passed to lower level functions

Value

The output from print.teqrOCtox is a listing of the operating characteristics for the design as specified by the user.

Author(s)

M.S. Blanchard <sblanchard@coh.org>

Examples

```
set.seed(1111)

OperChar<-teqrOCtox(
sim=500,
firstdose=2,
probt=c(0.05,0.15,0.23,0.34,0.51,0.76),
cohortSize=3,
MaxNoCohorts=30,
MTDss=12,
pTarget=0.2,
eq1=0.05,
eq2=0.05,
tootoxic=0.34)
OperChar
```

---

teqr.DLdata	*teqrOCtox intermediate file that creates dose level data*

Description

teqr.DLdata takes the simData output and creates the dose level data.

Usage

```
teqr.DLdata(simData = simData)
```

Arguments

simData   includes the simulation results data,simresult, cohortSize,probt, MTDss, pTarget, lowerlimit, upperlimit,tootoxic, the number of simulation (sim)

Author(s)

M.S. Blanchard <sblanchard@coh.org>

References

Blanchard MS and Longmate JA, (2011). Toxicity equivalence range design (TEQR): A practical Phase I design. *Contemporary Clinical Trials,(32)*, 114-121.

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teqr.DLdataconACT   *teqrOCact intermediate file that creates dose level data*

Description

teqr.DLdata takes the simData output and creates the dose level data.

Usage

```
teqr.DLdataconACT(simData = simData)
```

Arguments

simData   includes the simulation results data, cohortSize,proba,probc, MTDss,pTarget,lowerlimit,upperlimit,tootox
                 toxcon, llactivity, number of simulations (sim)

Author(s)

M.S. Blanchard <sblanchard@coh.org>

References

Blanchard MS and Longmate JA, (2011). Toxicity equivalence range design (TEQR): A practical
Phase I design. *Contemporary Clinical Trials,(32)*, 114-121.

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teqr.MTDdataconACT   *teqrOCact intermediate file that creates MTD/RP2D level data*

Description

teqr.MTDdatatox takes the simData and DLdata output and creates the MTD level data.

Usage

```
teqr.MTDdataconACT(simData = simData, DLdata = DLdata)
```

Arguments

simData   includes the simulation results data, cohortSize,proba,probc, MTDss,pTarget,lowerlimit,upperlimit,tootox
                 toxcon, llactivity, number of simulations (sim)

DLdata   simNo,doselevel,stox (no of subjects experiencing activity),dllength (length of
                 the cohort),toxl (lower 95% CI),toxu (upper 95% CI) ,toxCest (toxicity estimate)

Author(s)

M.S. Blanchard <sblanchard@coh.org>

References

Blanchard MS and Longmate JA, (2011). Toxicity equivalence range design (TEQR): A practical Phase I design. *Contemporary Clinical Trials,(32)*, 114-121.

---

teqr.MTDdatatox	*teqrOCtox intermediate file that creates MTD level data*

Description

teqr.MTDdatatox takes the simData and DLdata output and creates the MTD level data.

Usage

```
teqr.MTDdatatox(simData = simData, DLdata = DLdata)
```

Arguments

simData	includes the simulation results data,simresult, cohortSize,probt, MTDss, pTarget, lowerlimit, upperlimit,tootoxic, the number of simulation (sim)
DLdata	simNo,doselevel,stox (no of subjects experiencing a toxicity),dllength (length of the cohort),toxl (lower 95% CI),toxu (upper 95% CI) ,toxest (toxicity estimate)

Author(s)

M.S. Blanchard <sblanchard@coh.org>

References

Blanchard MS and Longmate JA, (2011). Toxicity equivalence range design (TEQR): A practical Phase I design. *Contemporary Clinical Trials,(32)*, 114-121.

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teqrDG	*TEQR Design Dose Escalation/Expansion/De-escalation Guidelines*

Description

teqrDG prints the TEQR Design Dose Escalation/Expansion/De-escalation Guidelines.

The toxicity equivalence range (TEQR) design, is a frequentist up-down design patterned after the modified toxicity probability interval design. The TEQR design extends the well known 3+3 design to allow for: an explicit target range for the dose limiting toxicity (DLT) rate, more than 6 subjects at the maximum tolerated dose (MTD), and specification of a too-toxic rate, which closes a dose level.

The TEQR is better than the 3+3 when compared on: 1) the number of times the dose at or nearest the target toxicity level was selected as the MTD, 2) the number of subjects assigned to doses levels,

at, or nearest the MTD, and 3) the overall trial DLT rate. For sample sizes at the MTD greater that 6 TEQR more accurately and more precisely estimates the rate of toxicity at the MTD because a larger number of subjects are studied at the MTD dose. The TEQR on average uses fewer subjects and provide reasonably comparable results to the continual reassessment method (CRM) in the number of times the dose at or nearest the target toxicity level was selected as the MTD and the number of subjects assigned doses, at, or nearest that target and in overall DLT rate.

Usage

```
teqrDG(TotalN,pTarget,eq1,eq2,tootoxic)
```

Arguments

TotalN	Total Number of subjects being considered at a dose level
pTarget	Target toxicity probability at the MTD.
eq1	Range subtracted from pTarget to achieve the lower boundary for the equivalence range.
eq2	Range added to pTarget to achieve the upper boundary for the equivalence range.
tootoxic	Probability cutoff at which the toxicity probability is deemed too high to allow further study at that dose level.

Value

TEQR outputs a table of dose escalation guidelines (DoseGuideTable) and a table of the underlying probabilities (ProbTable).

Author(s)

M.S. Blanchard <sblanchard@coh.org>

References

Blanchard MS and Longmate JA, (2011). Toxicity equivalence range design (TEQR): A practical Phase I design. *Contemporary Clinical Trials,(32)*, 114-121.

Examples

```
output<-teqrDG(TotalN=12,pTarget=0.2,eq1=0.05,eq2=0.05,tootoxic=0.34)
output
```

---

teqrOCact | *Activity Constrained for Toxicity (ACT) design trial simulator*

Description

The activity constrained for toxicity (ACT) design implements a cumulative cohort design in conjunction with safety rules similar to those from the toxicity equivalence range design or the modified toxicity probability interval design. The unique feature of this design is that dose is escalated based on lack of activity rather than on lack of toxicity and is de-escalated only if an unacceptable level of toxicity is experienced.

Usage

```
teqrOCact(sim,firstdose,proba,probc,cohortSize,MaxNoCohorts,
RP2Dss,pTarget,eq1,eq2,tootoxic,toxcon,llactivity)
```

Arguments

sim	Number of trial simulations desired. We recommend at least 1000. The example runs 500 to meet R package time limits.
firstdose	Dose level where the trial will start. The default setting is 2.
proba	Vector of activities associated with the dose elvels from 1 to n
probc	Vector of toxicities associated with the dose levels from 1 to n (e.g probt=c(0.05,0.15,0.23,0.34,0.51,0.76) for dose levels 1 to 6.)
cohortSize	Number of subjects per cohort. The default setting is 3.
MaxNoCohorts	Highest number of cohorts possible. The default setting is 30.
RP2Dss	Desired sample size at the recommended phase 2 dose (RP2D). The default setting is 12.
pTarget	Target activity probability at the RP2D.
eq1	Range subtracted from pTarget to achieve the lower boundary for the equivalence range.
eq2	Range added to pTarget to achieve the upper boundary for the equivalence range.
tootoxic	Toxicity probability deemed too high to allow further study at a dose level. Default is set to 1.01 and should not be changed in studing the ACT design.
toxcon	toxicity constaint level
llactivity	Required lower limit of activity to end the trial

Value

teqrOCact outputs the trial simulation operating characteristics, the simulation data sets, and all the simulation parameters. The simulation operating characteristics include, i) the average number of subjects studied at each dose level, ii) the rate the dose level is chosen as the RP2D (including if there is no RP2D identified), iii) median study sample size, iv) mean study event rate, v) mean event

rate at the RP2D, vi) mean 95% confidence interval length for the event rate at the RP2D, vii) mean toxicity rate at the the RP2D, viii) proportion of the trials with sample size at or above the level desired at the RP2D, viii) number of simulated trials that do not determine an RP2D and ix) number of simulated trials.

Datasets:

simData$simresults gives a line of data for each cohort. The columns are: simNo - simulation number, doselevel - dose level, act - the number of subjects that achieve the activity endpoint in the cohort, toxC - the number of subjects that experience a toxicity in the cohort, cumact - the cumulative rate of subjects achieving the activity endpoint at that dose level, and cumtoxC - the cumulative rate of subjects experiencing toxicity at that dose level.

DLdata gives a line of data for each dose level. The columns are: simNo - simulation number, doselevel - dose level, sact - sum of the number of subjects that achieve the activity endpoint at that doselevel, stoxC - sum of the number of subjects that experience the toxicity endpoint at that dose level, dllength - number of subjects studied at a doselevel, actl - lower limit of the 95% confidence limits for the activity rate, actu - upperlimit of the 95% confidence limits for the activity rate, actest - activity rate estimate at that doselevel, and toxCests - toxicity rate estimate at that doselevel.

RP2Ddata gives a line of data at the RP2D dose selected. The columns names are the same as for DLdata.

Author(s)

M.S. Blanchard <sblanchard@coh.org>

Examples

```
set.seed(1111)
OperChar<-teqrOCact(
sim=500,
firstdose=2,
proba=c(0.65,0.75,0.85,1.00),
probc=c(0.10,0.20,0.30,0.40),
cohortSize=3,
MaxNoCohorts=30,
RP2Dss=12,
pTarget=1.00,
eq1=0.34,
eq2=0.0,
toxcon=0.34,
llactivity=0.66)
OperChar
```

---

teqrOCtox   *TEQR Design trial simulator*

Description

teqrOCtox: Runs clinical trial simulations for the TEQR Design implemented as a Phase I toxicity design and provides a listing of the operating characteristics.

The toxicity equivalence range (TEQR) design is a frequentist up-down design patterned after the modified toxicity probability interval design. The TEQR design extends the well known 3+3 design to allow for: an explicit target range for the dose limiting toxicity (DLT) rate, more than 6 subjects at the maximum tolerated dose (MTD), and specification of a too-toxic rate, which closes a dose level.

The TEQR is better than the 3+3 when compared on: 1) the number of times the dose at or nearest the target toxicity level was selected as the MTD, 2) the number of subjects assigned to doses levels, at, or nearest the MTD, and 3) the overall trial DLT rate. For sample sizes at the MTD greater that 6 TEQR more accurately and more precisely estimates the rate of toxicity at the MTD because a larger number of subjects are studied at the MTD dose. The TEQR on average uses fewer subjects and provide reasonably comparable results to the continual reassessment method (CRM) in the number of times the dose at or nearest the target toxicity level was selected as the MTD and the number of subjects assigned doses, at, or nearest that target and in overall DLT rate.

Usage

```
teqrOCtox(sim,firstdose,probt,cohortSize,MaxNoCohorts,MTDss,pTarget,eq1,eq2,tootoxic)
```

Arguments

sim	Number of trial simulations desired. We recommend at least 1000. The example runs 500 to meet R package time limits.
firstdose	Dose level where the trial will start. The default setting is 2.
probt	Vector of toxicities associated with the dose levels from 1 to n (e.g probt=c(0.05,0.15,0.23,0.34,0.51,0.76) for dose levels 1 to 6.). We recommend that there be at least 4 dose levels with at least one level below and one level above the level expected to be at the target toxicitiy probability.
cohortSize	Number of subjects per cohort. The default setting is 3.
MaxNoCohorts	Highest number of cohorts possible. The default setting is 30.
MTDss	Desired sample size at the MTD. The default setting is 12.
pTarget	Target toxicity probability at the MTD.
eq1	Range subtracted from pTarget to achieve the lower boundary for the equivalence range.
eq2	Range added to pTarget to achieve the upper boundary for the equivalence range.
tootoxic	Toxicity probability deemed too high to allow further study at a dose level.

Value

teqrOC outputs the trial simulation operating characteristics, the simulation data sets, and all the simulation parameters. The simulation operating characteristics include, i) the average number of subjects studied at each dose level, ii) the rate the dose level is chosen as the MTD (including if there is no MTD identified), iii) median study sample size, iv) mean study DLT rate, v) mean DLT rate at

the MTD, vi) mean 95% confidence interval length for the DLT rate at the MTD, vii) proportion of the trials with sample size at or above the level desired at the MTD, viii) number of simulated trials that do not determine an MTD and ix) number of simulated trials.

Datasets:

simData$simresults gives a line of data for each cohort. The columns are: simNo - simulation number, doselevel - dose level, tox - the number of subjects the experience a toxicity in the cohort, and cumtox - cumulative toxicity in the cohort.

DLdata gives a line of data for each dose level. The columns are: simNo - simulation number, doselevel - dose level, stox - sum of the number of subjects that experience a toxicity at that doselevel, dllength - number of subjects studied at a doselevel, toxl - lower limit of the 95% confidence limits for toxicity rate, toxu - upperlimit of the 95% confidence limits for toxicity rate, and toxest - toxicity rate estimate at that doselevel.

MTDdata gives a line of data at the MTD dose selected. The columns names are the same as for DLdata.

Author(s)

M.S. Blanchard <sblanchard@coh.org>

References

Blanchard MS and Longmate JA, (2011). Toxicity equivalence range design (TEQR): A practical Phase I design. *Contemporary Clinical Trials,(32)*, 114-121.

Examples

```
set.seed(1111)
OperChar<-teqrOCtox(
sim=500,
firstdose=2,
probt=c(0.05,0.15,0.23,0.34,0.51,0.76),
cohortSize=3,
MaxNoCohorts=30,
MTDss=12,
pTarget=0.2,
eq1=0.05,
eq2=0.05,
tootoxic=0.34)
OperChar
```

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