Package 'SubTite'

July 2, 2020

Type Package

Title Subgroup Specific Optimal Dose Assignment

Version 3.0.2

Author Andrew Chapple

Maintainer Andrew Chapple <achapp@lsuhsc.edu>

Description

Chooses subgroup specific optimal doses in a phase I dose finding clinical trial allowing for subgroup combination and simulates clinical trials under the subgroup specific time to event continual reassessment method. Chapple, A.G., Thall, P.F. (2018) <doi:10.1002/pst.1891>.

License GPL-2

Imports Rcpp (>= 0.12.18)

LinkingTo Rcpp, RcppArmadillo

Encoding UTF-8

RoxygenNote 6.1.1

NeedsCompilation yes

Repository CRAN

Date/Publication 2020-07-02 04:20:03 UTC

R topics documented:

GetESS *Determines Prior ESS for fixed values of sigma_alpha^2 and sigma-beta^2*

Description

Uses the prior means for the intercept and slope parameters and the number of doses to obtain an approximate prior ESS for the given prior variances. The user should calibrate varint and varbeta with varint>varbeta such that the ESS value is 1.

Usage

```
GetESS(Dose, meanmu, meanslope, MeanInts, MeanSlopes, varint, varbeta)
```

Arguments

Dose	Vector containing standardized doses.
meanmu	Prior mean for baseline intercept.
meanslope	Prior mean for baseline slope.
MeanInts	Vector of prior means for the group specific intercept parameters.
MeanSlopes	Vector of prior means for the group specific slope parameters.
varint	Prior variance for the intercept parameters.
varbeta	Prior variance for the slope parameters.

Value

Returns the nonlinear regression model whos parameter estimates will be used as prior means for the SubTITE Design.

References

[1] Chapple and Thall (2017), Subgroup-specific dose finding in phase I clinical trials based on time to toxicity allowing adaptive subgroup combination.

Examples

```
###Specify the prior hypermeans
meanmu=-.5
meanslope=-.05
MeanInts = c(-.5,-.1)
MeanSlopes = c(.1,0)
Dose=sort(rnorm(5))
varint=5
varbeta=1
GetESS(Dose,meanmu,meanslope,MeanInts,MeanSlopes,varint,varbeta)
```

GetParams *Obtains true simulation parameters for each supported distribution function to correspond to a probability of the truth by time T1.*

Description

Obtains true simulation parameters for each supported distribution function to correspond to a probability of the truth by time T1.

Usage

```
GetParams(Family, ParamNum, Param, GroupProb, T1)
```

Arguments

Family	What distribution Family to simulate from. Options include: Exponential,Gamma, Lognormal, Uniform, Weibull.
ParamNum	Parameter index for user set value.
Param	#Groups X #Doses Matrix containing one parameter for each subgroup and dose.
GroupProb	#Groups X #Doses Matrix containing the true toxicity probability by time T1.
T1	Toxicity observation window.

Value

A list containing the hyperparameter matrices to input into the SimTrial function. Also plots the hazard of toxicity for each subgroup and dose.

Examples

```
GroupProb =matrix(c(.05,.3,.6,.7,.8,.01,.02,.13,.27,.5),nrow=2,byrow=TRUE)
##True Simulation distribution
Family="Weibull"
T1=6
Param = GroupProb*0 + 4 ##Late onset weibull
SimTruth = GetParams("Weibull",1,Param,GroupProb,T1)
```

`GetPriorMeans` *Calibrates prior means for Dose Finding Trial*

Description

Uses the clinician elicited prior reference probabilities for each subgroup and dose to obtain prior means for the Bayesian logistic regression model used in the SubTite trial design.

Usage

```
GetPriorMeans(Clinician, Dose)
```

Arguments

`Clinician`	#Groups X #Doses matrix containing the elicited prior toxicity probabilities at the reference time for each dose and subgroup.
`Dose`	Vector containing standardized doses.

Value

Returns the nonlinear regression model whos parameter estimates will be used as prior means for the SubTITE Design.

References

[1] Chapple and Thall (2017), Subgroup-specific dose finding in phase I clinical trials based on time to toxicity allowing adaptive subgroup combination

Examples

```
##Specify elicited reference toxicity probabilities
Clinician = matrix(c(.2,.3,.4,.5,.6,.1,.2,.3,.4,.5,.05,.1,.15,.2,.3),byrow=TRUE,nrow=3)
Dose=sort(rnorm(5))
GetPriorMeans(Clinician,Dose)
```

`GetSubTite` *Gives the subgroup specific optimal dose vector. Returns a list containing the optimal doses to enroll each subgroup at and the subgroups that should have their accrual suspended temporarily.*

Description

Gives the subgroup specific optimal dose vector. Returns a list containing the optimal doses to enroll each subgroup at and the subgroups that should have their accrual suspended temporarily.

Usage

```
GetSubTite(Y, I, Doses, Groups, DoseTried, cohort, T1, Target, Upper, Dose,
  meanmu, meanslope, MeanInts, MeanSlopes, varint, varbeta, phetero,
  Borrow, B)
```

Arguments

Y	Vector containing observed event or censoring times.
I	Vector containing event indicators (1 if patient experiences an event for a patient).
Doses	Vector containing Doses of patients in trial.
Groups	Vector containing group assignment of patients, 1 is baseline group.
DoseTried	Matrix that contains counts in each subgroup for the number of times each dose has been assigned.
cohort	Number of patients needed to be assigned at a dose level prior to escalation.
T1	Reference time for toxicity.
Target	Target cumulative toxicity probability vector at time T1.
Upper	Cutoff values used to determine if accrual in a subgroup should be suspended.
Dose	Vector containing the standardized doses considered.
meanmu	Prior mean for baseline intercept.
meanslope	Prior mean for baseline slope.
MeanInts	Vector of prior means for the group specific intercept parameters.
MeanSlopes	Vector of prior means for the group specific slope parameters.
varint	Prior variance for the intercept parameters.
varbeta	Prior variance for the slope parameters.
phetero	Prior probability of heterogeneous subgroups.
Borrow	Parameter to specify subgroup borrowing/clustering. 0=No borrowing, 1=Borrowing but no clustering, 2=Borrowing and clustering.
B	Number of Iterations to run for MCMC

Value

Returns a list with two objects, a vector of optimal doses for each subgroup and matrix of posterior toxicity probabilities at each dose level within each subgroup.

References

[1] Chapple and Thall (2017), Subgroup Specific Dose Finding in Phase I Clinical Trials Based on Time to Toxicity Within a Fixed Follow Up Period.

Examples

```
T1=6
## Reference Time for Toxicity
##Number of subgroups
nGroups=3
##Number of Doses
nDose=4
##What is the starting dose? We want to set all dose tried > cohort that's less than this
DoseStart=4
##Sample Size
n=90
Target=rep(.3,nGroups)
Upper=rep(.95,nGroups)
Y=rep(NA,n)
I=rep(NA,n)
Groups = sample(1:nGroups,n,replace=TRUE) - 1
##Group assignment of patients (MUST BE CODED 0,1,2,...)
Doses = sample(1:DoseStart,n,replace=TRUE)
Dose2=Doses ##Going to hold the numeric dose numbers
##Randomly Generate Dose values
x=sort(runif(nDose))  ##Doses are in ascending order
Dose=(x-mean(x))/sd(x)
##Vector of standardized doses
##Randomly generate TRUE group probabilties
GroupProb = matrix(ncol=nDose,nrow=nGroups)
for(k in 1:nGroups){
GroupProb[k,]=sort(runif(nDose,0,Target[k]+.2))
}
##Randomly generate patient data from a uniform TTE dist with given probabilities.
for(b in 1:n){
I[b]= rbinom(1,1   , GroupProb[(Groups[b]+1),Dose2[b]])
if(I[b]==0){ Y[b]=T1 }else{ Y[b]=runif(1,0,T1) }}
##How many patients in each subgroup have been assigned at each dose level?
DoseTried=cbind(table(Groups,Doses))
cohort=1 ##Cohort size required for escalation
##Matrix of umber of patients tried or fully evaluated at each dose level.
DoseTried[,1:DoseStart]=cohort
##Hyperparameters
meanmu=-0.4467184 ##Common Intercept hypermean
meanslope= 0.8861634 ##Common slope hypermean
MeanInts = rep(-0.5205379,nGroups-1) ##Group Intercept hypermeans
MeanSlopes = rep(0.1888923,nGroups-1) ##Group slope hyperneabs
Dose2=Doses ##Numeric Doses
Doses=Dose[Doses]  ##Standardize dose value
varint=5 #Prior Variance of the intercept betas
varbeta=1 ##Prior Variance of slope betas
phetero=.9 ##Prior Probability of hetergeneity
Borrow=0 ##Borrowing specification, 0=none, 1=some, 2=clustering.
B=5000 ##Number of iterations
Borrow=2
GetSubTite(Y, I,Doses, Groups, DoseTried,cohort, T1,
        Target,  Upper, Dose,  meanmu, meanslope,
```

```
MeanInts,  MeanSlopes ,varint,varbeta,phetero, Borrow,B)
```

MCMC *Performs MCMC and returns needed values for dose-finding in a list.*

Description

Performs MCMC and returns needed values for dose-finding in a list.

Usage

```
MCMC(Y, I, Doses, Groups, T1, Target, Upper, Dose, meanmu, meanslope,
  MeanInts, MeanSlopes, varint, varbeta, phetero, Stopped, NumPat, SubRout,
  B)
```

Arguments

Y	Vector containing observed event or censoring times.
I	Vector containing event indicators (1 if patient experiences an event for a patient).
Doses	Vector containing Doses of patients in trial.
Groups	Vector containing group assignment of patients, 0 is baseline group.
T1	Reference time for toxicity.
Target	Target cumulative toxicity probability vector at time T1.
Upper	Cutoff values used to determine if accrual in a subgroup should be suspended.
Dose	Vector containing the standardized doses considered.
meanmu	Prior mean for baseline intercept.
meanslope	Prior mean for baseline slope.
MeanInts	Vector of prior means for the group specific intercept parameters.
MeanSlopes	Vector of prior means for the group specific slope parameters.
varint	Prior variance for the intercept parameters.
varbeta	Prior variance for the slope parameters.
phetero	Prior probability of heterogeneous subgroups.
Stopped	Current vector of STOPPED groups
NumPat	Number of patients
SubRout	Parameter to specify subgroup borrowing/clustering. 0=No borrowing, 1=Borrowing but no clustering, 2=Borrowing and clustering.
B	Number of Iterations to run for MCMC

Value

A list of quantities needed for determining the next dose to enroll each subgroup.

MCMCSIM *Performs MCMC and returns needed values for dose-finding in a list.*

Description

Performs MCMC and returns needed values for dose-finding in a list.

Usage

```
MCMCSIM(Y, I, Doses, Groups, T1, Target, Upper, Dose, meanmu, meanslope,
  MeanInts, MeanSlopes, varint, varbeta, phetero, Stopped, NumPat, SubRout,
  B)
```

Arguments

Y	Vector containing observed event or censoring times.
I	Vector containing event indicators (1 if patient experiences an event for a patient).
Doses	Vector containing Doses of patients in trial.
Groups	Vector containing group assignment of patients, 0 is baseline group.
T1	Reference time for toxicity.
Target	Target cumulative toxicity probability vector at time T1.
Upper	Cutoff values used to determine if accrual in a subgroup should be suspended.
Dose	Vector containing the standardized doses considered.
meanmu	Prior mean for baseline intercept.
meanslope	Prior mean for baseline slope.
MeanInts	Vector of prior means for the group specific intercept parameters.
MeanSlopes	Vector of prior means for the group specific slope parameters.
varint	Prior variance for the intercept parameters.
varbeta	Prior variance for the slope parameters.
phetero	Prior probability of heterogeneous subgroups.
Stopped	Current vector of STOPPED groups
NumPat	Number of patients
SubRout	Parameter to specify subgroup borrowing/clustering. 0=No borrowing, 1=Borrowing but no clustering, 2=Borrowing and clustering.
B	Number of Iterations to run for MCMC

Value

A matrix of quantities needed for determining the next dose to enroll each subgroup while using the SimTrial function.

SimTrial *Simulates a Sub-TITE trial design*

Description

Simulates replicates from a Sub-TITE trial with user specified true toxicity time distributions for different doses and subgroups and returns average summary statistics of the trial.

Usage

```
SimTrial(nSims, Nmax, T1, Target, Dose, DoseStart, Upper, Accrue,
  groupprob, meanmu, meanslope, MeanInts, MeanSlopes, VarInt, VarSlope,
  phetero, Family, SimTruth, NSep, NBorrow, cohort, FULL)
```

Arguments

nSims	Number of Trials to Simulate.
Nmax	Maximum Number of Patients to enroll in the trial.
T1	Reference time for toxicity.
Target	Target cumulative toxicity probability (or subgroup specific vector) at time T1.
Dose	Standardized vector of doses to try.
DoseStart	Dose (or vector of Doses) to enroll the first patient in each subgroup at.
Upper	Cutoff values used to determine if accrual in a subgroup should be suspended.
Accrue	Expected montly patient accrual rate.
groupprob	Probability vector of subgroup assignment.
meanmu	Prior mean of the baseline intercept parameter.
meanslope	Prior mean of the baseline slope parameter.
MeanInts	G-1 length vector of subgroup specific prior intercept means.
MeanSlopes	G-1 length vector of subgroup specific prior slope means.
VarInt	Prior Variance of Intercept Parameters.
VarSlope	Prior Variance of Slope Parameters.
phetero	Prior prob of clustering
Family	What distribution Family to simulate from. Options include: Exponential,Gamma, Lognormal, Uniform, Weibull.
SimTruth	List of 2 #Groups by #Doses matrices containing the true parameter values needed for simulating from different true time to toxicity distributions.
NSep	Number of patients to assign based on no borrowing.
NBorrow	Number of patients to assign based on no clustering
cohort	Number of patients to enroll before escalating.
FULL	Do we have to fully evaluate a cohort before escalating?

Value

A list with first entry corresponding to summaries of the operating characteristics of the design including

Examples

```
##Note: nSims  should be set larger than the example below.
nSims=1
###TRIAL PARAMETERS###
##Specify reference toxicity time and target
T1=6
Target=.3
##Number of Groups
##Specify upper bound for determining if the lowest dose is too toxic in a subgroup
Upper=c(.95,.95)
#' ##Standardized Dose Values and starting dose index
Dose=sort(rnorm(5))
DoseStart=1
##Maximum Sample Size
Nmax=25
##Number of patients to run separately
NSep=0
##Number of patients to borrow, but NOT cluster
NBorrow=0
##Number of patients to fully evaluate or TREAT before ESCALATING
cohort=3
##Do we fully evaluate a cohort before escalating?
FULL=0
#HYPERPARAMETERS#
##Hypermeans for baseline terms
meanmu=2.21
meanslope=-.57
##Hypervectors for subgroup specific terms
MeanInts = c(.46)
MeanSlopes = c(.04)
##Hypervariances
VarInt=5
VarSlope=1
######SIMULATION TRUTH####
##True Accrual Rate
Accrue=2
##True Distribution of subgroups
groupprob=c(.5,.5)
##True Group Toxicity probabilities at each dose level
GroupProb =matrix(c(.05,.3,.6,.7,.8,.01,.02,.13,.27,.5),nrow=2,byrow=TRUE)
##True Simulation distribution
Family="Uniform"
SimTruth = as.list(c(0,0))
SimTruth[[1]]=GroupProb
SimTruth[[2]]=GroupProb
phetero=.9
RESULTS=SimTrial(nSims,Nmax,T1,Target,Dose,DoseStart,
```

```
Upper,Accrue,groupprob,meanmu,meanslope,
MeanInts,MeanSlopes,VarInt,VarSlope,phetero,
Family,SimTruth,NSep,NBorrow,cohort,FULL)
RESULTS[[1]]
```

SimTrial1 *Simulates a Sub-TITE trial design*

Description

Simulates replicates from a Sub-TITE trial with user specified true toxicity time distributions for different doses and subgroups and returns average summary statistics of the trial.

Usage

```
SimTrial1(nSims, Nmax, T1, Target, Dose, DoseStart, Upper, Accrue,
  groupprob, Family, Param1, Param2, meanmu, meanslope, MeanInts,
  MeanSlopes, varint, varbeta, phetero, NSep, NBorrow, cohort, FULLY)
```

Arguments

nSims	Number of Trials to Simulate.
Nmax	Maximum Number of Patients to enroll in the trial.
T1	Reference time for toxicity.
Target	Target cumulative toxicity probability (or subgroup specific vector) at time T1.
Dose	Standardized vector of doses to try.
DoseStart	Dose (or vector of Doses) to enroll the first patient in each subgroup at.
Upper	Cutoff values used to determine if accrual in a subgroup should be suspended.
Accrue	Expected montly patient accrual rate.
groupprob	Probability vector of subgroup assignment.
Family	What distribution Family to simulate from. Options include: Exponential,Gamma, Lognormal, Uniform, Weibull.
Param1	nGroups X nDose matrix of first parameter values.
Param2	NGroups X nDose matrix of second parameter values.
meanmu	Prior mean of the baseline intercept parameter.
meanslope	Prior mean of the baseline slope parameter.
MeanInts	G-1 length vector of subgroup specific prior intercept means.
MeanSlopes	G-1 length vector of subgroup specific prior slope means.
varint	Prior Variance of Intercept Parameters.
varbeta	Prior Variance of Slope Parameters.
phetero	Prior prob of heterogeneity.
NSep	Number of patients to assign based on no borrowing.
NBorrow	Number of patients to assign based on no clustering
cohort	Number of patients to enroll before escalating.
FULLY	Do we have to fully evaluate a cohort before escalating?

Value

A list of simulation outputs to be processed in R.

Index