Package 'SubTite'

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Type Package

Title Subgroup Specific Optimal Dose Assignment

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Description Contains functions for choosing subgroup specific optimal doses in a phase I dose finding clinical trial allowing for subgroup combination and simulating a clinical trial under the subgroup specific time to event continual reassessment method.

License GPL-2

Encoding UTF-8

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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)
```

`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, T1, Target, Upper, Dose, meanmu,
  meanslope, MeanInts, MeanSlopes, varint, varbeta)
```

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	#Groups X #Doses Matrix that contains 1s and 0s corresponding to whether a given dose in a subgroup had been tried.
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.#' @return Returns a list with two objects, a vector of optimal doses and a vector of stopped groups

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. [2] Package Tutorial, https://adventuresinstatistics.wordpress.com/2017/0
subtite-package-tutorial/

Examples

```
T1=6
##Reference Time for Toxicity
Target=.3
Upper=c(.95,.95)
n=30
Y=rep(NA,n)
I=rep(NA,n)
Groups = sample(1:2,n,replace=TRUE) - 1
##Group assignment of patients (MUST BE CODED 0,1,2,...)
Doses = sample(1:5,n,replace=TRUE)
##Randomly Generate Dose assignment
x=c(1,2,3,5,7)
```

```
Dose=(x-mean(x))/sd(x)
##Vector of standardized doses
##Next we generate the toxicity times based on a true toxicity probability matrix
GroupProb = matrix(rep(NA,length(Dose)*3),nrow=3)
GroupProb[1,]=c(.18,.25,.45,.66,.74)
 ## These are the true toxicity probabilities for each dose and subgroup
GroupProb[2,]=c(.10,.15,.30,.50,.60) +.1
for(b in 1:n){
I[b]= rbinom(1,1   , GroupProb[(Groups[b]+1),Doses[b]])
if(I[b]==0){ Y[b]=T1 }else{ Y[b]=runif(1,0,T1) }}
DoseTried=matrix(c(1,1,0,0,0,1,1,1,1,1),ncol=5,byrow=TRUE)
 ##Doses Tried so far in trial
##Hypermeans for linear terms
meanmu=-0.4467184
meanslope= 0.8861634
MeanInts = -0.5205379
MeanSlopes = 0.1888923
Doses=Dose[Doses]
varint=5
varbeta=1
GetSubTite(Y, I,Doses, Groups, DoseTried, T1,
 Target,  Upper, Dose,  meanmu, meanslope,
  MeanInts,  MeanSlopes ,varint,varbeta)
```

`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,
  Hyper, Family, Param1, Param2, VarInt, VarSlope)
```

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.
Hyper	List of size 4 containing the prior mean of the baseline slope, the baseline intercept, and the prior mean vectors for group specific intercepts and slopes.
Family	What distribution Family to simulate from. Options include: Exponential,Gamma, Lognormal, Uniform, Weibull.
Param1	#Groups X #Doses Matrix containing the first parameter for each subgroup and dose. For the uniform distribution, this is the probability of toxicity in a given group.
Param2	#Groups X #Doses Matrix containing the second parameter for each subgroup and dose for the Weibull, Gamma and Lognormal Distributions. This argument is not used for uniform and exponential distribution families.
VarInt	Prior Variance of Intercept Parameters
VarSlope	Prior Variance of Slope Parameters

Value

Returns a list with five simulation outputs: The vector of optimal doses chosen, the number of toxicities per group, the trial times of each simulated trial, the vector containing the doses administered in a trial and the group assignments of each patient in a simulated trial.

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

```
##Note: nSims  should be set larger than the example below.
nSims=1
##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)
##Maximum Sample Size
Nmax=40
##Standardized Dose Values and starting dose index
Dose=sort(rnorm(4))
DoseStart=1
##Hypermeans for linear terms
meanmu=2.21
meanslope=-.57
MeanInts = c(.46)
MeanSlopes = c(.04)
##Accrual Rate
Accrue=2
groupprob=c(.5,.5)
##Fill in Hyperparameter list for MCMC
```

```
Hyper=as.list(c(0,0,0,0))
Hyper[[1]]=meanmu
Hyper[[2]]=meanslope
Hyper[[3]]=MeanInts
Hyper[[4]]=MeanSlopes
Family="Uniform"
Param1 = matrix(c(.2,.3,.4,.5,.6,.1,.2,.3,.4,.5),byrow=TRUE,nrow=2)
Param2=Param1
VarInt=5
VarSlope=1
SimTrial(nSims,Nmax,T1,Target,Dose,DoseStart,
Upper,Accrue,groupprob,Hyper,Family,Param1,Param2,VarInt,VarSlope)
```

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