Package 'HCTDesign'

October 20, 2025

Title Group Sequential Design for Historical Control Trial with Survival Outcome

Version 0.7.4

Imports Rdpack, diversitree, mvtnorm, flexsurv, stats, survival, crayon

RdMacros Rdpack

Description

It provides functions to design historical controlled trials with survival outcome by group sequential method. The options for interim look boundaries are efficacy only, efficacy & futility or futility only. It also provides the function to monitor the trial for any unplanned look. The package is based on Jianrong Wu, Xiaoping Xiong (2016) <doi:10.1002/pst.1756> and Jianrong Wu, Yimei Li (2020) <doi:10.1080/10543406.2019.1684305>.

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Encoding UTF-8

RoxygenNote 7.3.2

NeedsCompilation no

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Repository CRAN

Date/Publication 2025-10-20 21:30:02 UTC

Contents

`calendar_time` *Calculate Calendar Times for Interim Analysis Looks*

Description

Calculate Calendar Times for Interim Analysis Looks

Usage

```
calendar_time(
  k,
  d2max,
  htime,
  hevent,
  delta,
  ta,
  tf,
  method = c("KM"),
  event_ind = 1
)
```

Arguments

`k`	Numeric vector of event fractions for each look (e.g., c(0.5, 1))
`d2max`	maximum number of events in the experimental group calculated from the design function.
`htime`	Historical survival times
`hevent`	Historical event indicators (0/1)
`delta`	Hazard ratio (experimental vs. historical)
`ta`	Accrual time
`tf`	Follow-up time
`method`	"exponential", "log_normal" or "KM" for survival function estimation(Default is KM)
`event_ind`	Event indicator value (default = 1)

Value

Data frame with columns: Distribution, look, time fraction, events, calendar time

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
time <- c(20, 65, 12, 50, 58, 65, 45, 44)
event <- c(1, 0, 0, 0, 1, 1, 1, 1)
gg<-calendar_time(k=c(0.5, 1),d2max=46,htime=time,hevent=event,delta=0.7,ta=5,tf=4,method="KM")
```

`EffDesign` *HCT design with interim monitoring for efficacy only*

Description

The group sequential design for historical controlled survival outcome trials with efficacy boundaries only.

Usage

```
EffDesign(
  k,
  alpha,
  beta,
  delta,
  delta0,
  d1,
  option = "OBF",
  param = 4,
  trial = "Superiority"
)
```

Arguments

`k`	vector of time fraction for all planned looks: k=c(1/3,2/3,1) if the three planned looks will be carried out at 1/3, 2/3 and all of the total events in the experiment arm.
`alpha`	type I error.
`beta`	type II error.
`delta`	hazard ratio: hazard of experiment group over hazard of control group.
`delta0`	Non-inferiority margin.
`d1`	total number of events in the historical control group.

option	type of spending function: "OBF", "Gamma", "Rho" or "Pocock". Default is "OBF.
param	Parameter for Gamma family or Rho family. Default value is 4.
trial	Type of trial: "Superiority" or "Non-inferiority". Default is "Superiority".

Value

List of dataframes and vectors containing the details about the following: design of the trial which includes the number of looks and events; details about futility and efficacy boundaries which include transformed information time at each look, cumulative beta and alpha respectively, p-values and crossing probabilities; etam(drift parameter); d2max(maximum number of events in the experimental group); delta_used(hazard ratio used in the design).

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
#Superiority trial with three equally spaced looks for efficacy using OBF spending function.
gg<-EffDesign(k=c(0.3,0.6,1),alpha=0.05,beta=0.1,delta=0.57,d1=65,option="OBF",trial="Superiority")
```

EffIM *Monitoring the trial at interim looks for a trial with efficacy monitoring only*

Description

Calculates one-sided efficacy boundary values at the observed number of events.

Usage

```
EffIM(
  d2,
  dmax,
  last.look = FALSE,
  d1,
  etam,
  alpha,
  beta,
```

```
  opt = "OBF",
  param = 4
)
```

Arguments

d2	vector of number of events at which you want to monitor the trial.
dmax	maximum number of events in the experimental group calculated from design function.
last.look	logical which indicates whether the current look is the last look or not. Default is FALSE. If true, the post hoc power is calculated.
d1	total number of events in the historical control group.
etam	value of the drift parameter obtained from design function.
alpha	type I error.
beta	type II error.
opt	type of spending function: "OBF", "Gamma", "Rho" or "Pocock". Default is "OBF".
param	Parameter for "gamma family" or rho family. Default value is 4.

Details

The number of events have to be entered sequentially. See example.

Value

A list containing efficacy boundary values along with the p-values and transformed information time for the current look. Post-hoc power is also calculated in case of early stopping of the trial.

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
#Interim look for the trial when the number of events is 13(first look).
gg<-EffIM(c(13),dmax=57,alpha=0.05,beta=0.1,etam=3.0726,d1=65,opt="OBF",last.look=FALSE)
#Interim look for the trial when the number of events is 35(second look).
gg<-EffIM(c(13,35),dmax=57,alpha=0.05,beta=0.1,etam=3.0726,d1=65,opt="OBF",last.look=FALSE)
```

FutDesign *HCT design with interim monitoring for futiity only*

Description

The group sequential design for historical controlled survival outcome trials with futility boundaries only.

Usage

```
FutDesign(
  k,
  alpha,
  beta,
  delta,
  d1,
  option = "OBF",
  param = 4,
  trial = "Superiority",
  delta0
)
```

Arguments

k	vector of time fraction for all planned looks: k=c(1/3,2/3,1) if the three planned looks will be carried out at 1/3, 2/3 and all of the total events in the experiment arm.
alpha	type I error.
beta	type II error.
delta	hazard ratio: hazard of experiment group over hazard of control group.
d1	total number of events in the historical control group.
option	type of spending function: "OBF", "Gamma", "Rho" or "Pocock". Default is "OBF.
param	Parameter for Gamma family or Rho family. Default value is 4.
trial	Type of trial: "Superiority" or "Non-inferiority". Default is "Superiority".
delta0	Non-inferiority margin.

Value

List of dataframes and vectors containing the details about the following: design of the trial which includes the number of looks and events; details about futility and efficacy boundaries which include transformed information time at each look, cumulative beta and alpha respectively, p-values and crossing probabilities; etam(drift parameter); d2max(maximum number of events in the experimental group); delta_used(hazard ratio used in the design).

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
#Sequential superiority trial for three equally spaced looks for OBF spending function.
gg<-FutDesign(k=c(0.3,0.6,1),alpha=0.05,beta=0.1,delta=0.57,d1=65,option="OBF",trial="Superiority")
```

FutIM *Monitoring the trial at interim looks for a trial with futility monitoring only*

Description

Calculates one-sided futility boundary values at the observed number of events.

Usage

```
FutIM(
  d2,
  dmax,
  last.look = FALSE,
  d1,
  etam,
  alpha,
  beta,
  opt = "OBF",
  param = 4
)
```

Arguments

d2	vector of number of events at which you want to monitor the trial.
dmax	maximum number of events in the experimental group caculated from design function.
last.look	logical which indicates whether the current look is the last look or not. Default is FALSE.
d1	total number of events in the historical control group.
etam	value of the drift parameter obtained from design function.

alpha	type I error.
beta	type II error.
opt	type of spending function: "OBF", "Gamma", "Rho" or "Pocock". Default is "OBF".
param	Parameter for Gamma family or Rho family. Default value is 4.

Details

The number of events have to be entered sequentially. See example.

Value

A list containing futility boundary values along with the p-values and transformed information time for the current look.Post-hoc power is also calculated in case of early stopping of the trial.

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
#Interim look for the trial when the number of events is 13(first look).
gg<-FutIM(c(13),dmax=57,alpha=0.05,beta=0.1,etam=3.0726,d1=65,opt="OBF",last.look=FALSE)
#Interim look for the trial when the number of events is 35(second look).
gg<-FutIM(c(13,35),dmax=57,alpha=0.05,beta=0.1,etam=3.0726,d1=65,opt="OBF",last.look=FALSE)
```

HCTSurvDesign *HCT design with interim monitoring for both efficacy and futility*

Description

The group sequential design for historical controlled survival outcome trials with both efficacy and futility boundaries.

Usage

```
HCTSurvDesign(
  k,
  alpha,
  beta,
  delta,
  d1,
  option = "OBF",
  param = 4,
  trial = "Superiority",
  delta0
)
```

Arguments

k	vector of time fraction for all planned looks: k=c(1/3,2/3,1) if the three planned looks will be carried out at 1/3, 2/3 and all of the total events in the experiment arm.
alpha	type I error.
beta	type II error.
delta	hazard ratio: hazard of experiment group over hazard of control group.
d1	total number of events in the historical control group.
option	type of spending function: "OBF", "Gamma", "Rho" or "Pocock". Default is "OBF".
param	Parameter for Gamma family or Rho family. Default value is 4.
trial	Type of trial: "Superiority" or "Non-inferiority". Default is "Superiority".
delta0	Non-inferiority margin.

Value

List of dataframes and vectors containing the details about the following: design of the trial which includes the number of looks and events; details about futility and efficacy boundaries which include transformed information time at each look, cumulative beta and alpha respectively, p-values and crossing probabilities; etam(drift parameter); d2max(maximum number of events in the experimental group); delta_used(hazard ratio used in the design).

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
#Sequential superiority trial for three equally spaced looks for OBF spending function.
gg<-HCTSurvDesign(k=c(0.3,0.6,1),alpha=0.05,beta=0.1,delta=0.57,d1=65,option="OBF")
```

IM *Monitoring the trial at interim looks for a trial with efficacy and futility boundaries*

Description

Calculates one-sided boundary values at the observed number of events.

Usage

```
IM(d2, dmax, last.look = FALSE, d1, etam, alpha, beta, opt = "OBF", param = 4)
```

Arguments

d2	vector of number of events at which you want to monitor the trial.
dmax	maximum number of events in the experimental group calculated from design function.
last.look	logical which indicates whether the current look is the last look or not. Default is FALSE.
d1	total number of events in the historical control group.
etam	value of the drift parameter obtained from design function.
alpha	type I error.
beta	type II error.
opt	type of spending function: "OBF", "Gamma", "Rho" or "Pocock". Default is "OBF".
param	Parameter for Gamma family or Rho family. Default value is 4.

Details

The number of events have to be entered sequentially. See example.

Value

A list containing efficacy and futility boundary values along with the p-values and transformed information time for the current look. Post-hoc power is also calculated in case of early stopping of the trial.

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
#Interim look for the trial when the number of events is 13(first look).
gg<-IM(c(13),dmax=57,alpha=0.05,beta=0.1,etam=3.0726,d1=65,opt="OBF",last.look=FALSE)
#Interim look for the trial when the number of events is 35(second look).
gg<-IM(c(13,35),dmax=57,alpha=0.05,beta=0.1,etam=3.0726,d1=65,opt="OBF",last.look=FALSE)
```

---

sf *Log rank test for non-inferiority trial*

Description

Calculates the score function of the log rank test for non-inferiority trial

Usage

```
sf(event, status, delta0, group, experiment, control)
```

Arguments

`event`	event time vector from person level trial data.
`status`	numeric vector indicating the status of event from person level trial data.
`delta0`	Non-inferiority margin.
`group`	group string vector indicating the assignment of patients into control or experimental group.
`experiment`	name of experimental group as character string.
`control`	name of control group as character string.

Value

Returns the value of score statistic.

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

Examples

```
time<-c(20,65,12,50,58,65,45,44)
event<-c(1,0,0,0,1,1,1,1)
group<-c(rep("exp",4),rep("cont",4))
gg<-sf(event=time,status=event,delta0=1.3,group=group,experiment="exp",control="cont")
```

SM *Sample size in terms of number of subjects in the experimental group*

Description

Calculates the total number of subjects for the experimental group using the total number of events(d2max:the output from design functions) and the estimated failure probability based on the person level historical control data and proportional hazard assumption.

Usage

```
SM(time, event, d2max, opt = c("KM"), event_ind, ta, tf, delta)
```

Arguments

time	event time vector from person level historical control data.
event	numeric vector indicating the status of event from person level historical control data.
d2max	maximum number of events in the experimental group calculated from the design function.
opt	the method of fitting survival curve-"log_normal", "exponential or "KM" (log-normal, exponential or Kaplan Meier). Default is "KM".
event_ind	numeric value indicating the occurrence of event.
ta	enrollment time.
tf	follow-up time.
delta	hazard ratio.

Value

Returns the value of sample size.

Author(s)

Tushar Patni, Yimei Li and Jianrong Wu.

References

Wu J, Xiong X (2016). "Survival trial design and monitoring using historical controls." *Pharmaceutical Statistics*, **15**(5), 405-411.

Wu J, Li Y (2020). "Group sequential design for historical control trials using error spending functions." *Journal of Biopharmaceutical Statistics*, **30**(2), 351-363.

Examples

```
time<-c(20,65,12,50,58,65,45,44)
event<-c(1,0,0,0,1,1,1,1)
d2max=57
gg<-SM(time,event,d2max,opt="log_normal",ta=4,tf=3,delta=0.57,event_ind=1)
```

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