

# Package ‘sp23design’

February 20, 2015

**Type** Package

**Title** Design and Simulation of seamless Phase II-III Clinical Trials

**Version** 0.9

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**Maintainer** Balasubramanian Narasimhan <naras@stat.stanford.edu>

## Description

Provides methods for generating, exploring and executing seamless Phase II-III designs of Lai, Lavori and Shih using generalized likelihood ratio statistics. Includes pdf and source files that describe the entire R implementation with the relevant mathematical details.

**Depends** R (>= 3.0), mvtnorm, survival

**Suggests** RUnit

**License** LGPL-3

**NeedsCompilation** no

**Repository** CRAN

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sp23design-package	<i>sp23design: A package for the design, exploration and execution of seamless Phase II-II clinical trials</i>
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## Description

This package implements the methodology described in the paper below

## Details

Package:	sp23design
Type:	Package
Version:	1.0
Date:	2011-05-05
License:	LGPL?
LazyLoad:	yes

The most important functions in this package are [generateSP23Design](#), [exploreSP23Design](#), [executeSP23Design](#), and [analyzeSP23Design](#)

## Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He  
 Maintainer: Balasubramanian Narasimhan <naras@stat.stanford.edu>

## References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

## Examples

```
## Not run:
catn <- function(...) cat(..., "\n")

trialParameters <- list(minimumNumberOfEvents = 20,
```

```

        minimumIncreaseInV = 0.2,
        numberRecruitedEachYear = c(80, 120, 160, 160),
        followupTime = 3,
        adminCensoringTime = 7,
        interimLookTime = c(1, 2, 3, 5, 7),
        type1ErrorForResponse = 0.05,
        type2ErrorForResponse = 0.01,
        glrBoundarySidedness = "one", # one sided or two-sided
        type1Error = 0.05,
        type2Error = 0.10,
        epsType1 = 1/3,
        epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                      p1 = 0.3,
                      pdiffHyp=0.3,
                      theta = list(
                        alpha = 0,
                        beta = 0,
                        gamma = 0),
                      baselineLambda = 0.35,
                      etaHyp = 0.25)

rngSeed <- 9872831
sp23Design <- generateSP23Design(trueParameters, trialParameters)
print(sp23Design)
trialHistory <- exploreSP23Design(sp23Design, numberOfSimulations=25, rngSeed=rngSeed)
result <- analyzeSP23Design(sp23Design, trialHistory)$designSummary
catn("numberOfTimesH0RIsRejectedAtFirstLook", result[["numberOfTimesH0RIsRejectedAtFirstLook"]])
catn("numberOfTimesH0RIsRejected", result[["numberOfTimesH0RIsRejected"]])
catn("numberOfTimesStoppedForFutility", result[["numberOfTimesStoppedForFutility"]])
catn("numberOfTimesH0SIsAccepted", result[["numberOfTimesH0SIsAccepted"]])
catn("numberOfTimesH0SIsRejected", result[["numberOfTimesH0SIsRejected"]])
catn("numberOfTimesFutilityDecidedAtLastLook", result[["numberOfTimesFutilityDecidedAtLastLook"]])
catn("numberOfTimesTrialEndedAtLook", result[["numberOfTimesTrialEndedAtLook"]])
catn("avgExitTime", result[["avgExitTime"]])

## End(Not run)

```

---

analyzeSP23Design	<i>Analyses the results of running a design. If a trial history, such as the result of the function <code>executeSP23Design</code> or a history of the actual conduct of a single trial is provided, it returns the analysis results.</i>
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---

## Description

Produces analysis results from the run of a single trial or a number of simulations.

## Usage

```
analyzeSP23Design(sp23Design, trialHistory = NULL, data = NULL,
                 col=c("red", "red", "brown", "brown"), lty=c(1,2,1,2))
```

**Arguments**

sp23Design	The design object typically produced by calling <code>generateSP23Design</code> .
trialHistory	Typically the result of calling <code>executeSP23Design</code> which is a single data frame, or, the result produced by calling <code>exploreSP23Design</code> which is a list of data frames, one for each simulation.
data	This is only used when the argument <code>trialHistory</code> is a single data frame, in which case, it should be the data generated in the clinical trial.
col	Colors used for the survival plots
lty	Line types for the survival plots

**Details**

If `trialHistory` is a single data frame, the naive response estimates and a survival plot are produced. Otherwise, the counts of the number of times the various hypothesis are rejected and other details are returned.

**Value**

A list of two items named `responseSummary` and `designSummary`. If `trialHistory` is a single data frame, the naive response estimates are returned in `responseSummary` and a survival plot is produced. Otherwise, the counts of the number of times the various hypothesis are rejected and other details are returned in `designSummary`.

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

**Examples**

```
## Not run:
catn <- function(...) cat(..., "\n")

trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
                        type2Error = 0.10,
                        epsType1 = 1/3,
```

```

epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                      p1 = 0.3,
                      pdiffHyp=0.3,
                      theta = list(
                        alpha = 0,
                        beta = 0,
                        gamma = 0),
                      baselineLambda = 0.35,
                      etaHyp = 0.25)

rngSeed <- 9872831
sp23Design <- generateSP23Design(trueParameters, trialParameters)
print(sp23Design)
trialHistory <- exploreSP23Design(sp23Design, numberOfSimulations=25, rngSeed=rngSeed)
result <- analyzeSP23Design(sp23Design, trialHistory)$designSummary
catn("numberOfTimesH0RIsRejectedAtFirstLook", result[["numberOfTimesH0RIsRejectedAtFirstLook"]])
catn("numberOfTimesH0RIsRejected", result[["numberOfTimesH0RIsRejected"]])
catn("numberOfTimesStoppedForFutility", result[["numberOfTimesStoppedForFutility"]])
catn("numberOfTimesH0SIsAccepted", result[["numberOfTimesH0SIsAccepted"]])
catn("numberOfTimesH0SIsRejected", result[["numberOfTimesH0SIsRejected"]])
catn("numberOfTimesFutilityDecidedAtLastLook", result[["numberOfTimesFutilityDecidedAtLastLook"]])
catn("numberOfTimesTrialEndedAtLook", result[["numberOfTimesTrialEndedAtLook"]])
catn("avgExitTime", result[["avgExitTime"]])

## End(Not run)

```

---

computeDGivenXi

*Given the estimates of the  $\pi$  and  $\theta$ , compute  $d$ .*


---

### Description

This function computes  $d$  via

$$d(\pi, \xi) = \{\pi_0 a + (1 - \pi_0)\} - \{\pi_1 abc + (1 - \pi_1)b\}$$

### Usage

```
computeDGivenXi(piVec, xiVec)
```

### Arguments

piVec            The two-element vector of  $(\pi_0, \pi_1)$   
xiVec            The three-element vector of  $(a = e^\alpha, b = e^\beta, c = e^\gamma)$

### Details

This is an approximation to the hazard ratio

**Value**

The computed value of  $d$ , a scalar

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

computeGammaSubT	<i>Compute the estimate of the variance of the generalized likelihood ratio statistic at time <math>t</math></i>
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---

**Description**

This function computes the variance of the generalized likelihood ratio statistic at interim stopping times

**Usage**

```
computeGammaSubT(thetaHat, pi, interimData)
```

**Arguments**

thetaHat	The three-element vector of $(\alpha, \beta, \gamma)$
pi	The two-element vector of $(\pi_0, \pi_1)$
interimData	The interim data at time $t$ as a data frame

**Details**

The function builds a hessian matrix and uses a reparametrization to compute  $\Gamma_t$ , the variance of the generalized likelihood ration stochastic process at time  $t$ .

**Value**

A scalar value of the variance  $\Gamma_t$

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

 computeResponseSummary

*Given interim data, compute the response end-point summary*


---

### Description

Compute the response end-point summary for interim data. This will include the proportion of responses, the proportion of people on treatment and control etc.

### Usage

```
computeResponseSummary(interimData)
```

### Arguments

`interimData`      The interim data for the clinical trial

### Details

The result is a vector of counts and proportions

### Value

<code>m0</code>	number on control arm
<code>m1</code>	number on treatment arm
<code>y0</code>	number of responses in control
<code>y1</code>	number of responses in treatment
<code>numberOfTotalResponses</code>	number of total responses in both arms
<code>controlRespProp</code>	the proportion of responders in control arm
<code>treatmentRespProp</code>	the proportion of responders in the treatment arm
<code>pooledProp</code>	the pooled response proportion

### Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

### References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

**Examples**

```
## Not run:
trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
                        type2Error = 0.10,
                        epsType1 = 1/3,
                        epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                       p1 = 0.3,
                       pdiffHyp=0.3,
                       theta = list(
                         alpha = 0,
                         beta = 0,
                         gamma = 0),
                       baselineLambda = 0.35,
                       etaHyp = 0.25)

rngSeed <- 9872831

d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                              nFUp = trialParameters$followupTime,
                              pi0 = trueParameters$p0,
                              pi1 = trueParameters$p1,
                              theta = trueParameters$theta,
                              lambda0 = trueParameters$baselineLambda)

dInterim <- generateInterimData(d, trialParameters$interimLookTime[2],
                                trialParameters$adminCensoringTime)

computeResponseSummary(dInterim)

## End(Not run)
```

---

executeSP23Design

*Given a design object, interim data and the current calendar time,  
conduct the interim analysis for the time*

---

**Description**

This function is designed to be used in the field. Assuming a particular design is chosen, it conducts the interim analysis for a specific calendar time and provides the means for deciding whether to stop for futility or efficacy.



**Usage**

```
executeSP23Design(sp23DesignObject, data, currentCalendarTime)
```

**Arguments**

sp23DesignObject	A seamless phase II-III design object, typically one produced by the <a href="#">generateSP23Design</a> function
data	The interim data, something akin to that produced by the function <a href="#">generateInterimData</a>
currentCalendarTime	The current calendar time of the interim data. This better be one of the specified interim looks, or the function stops.

**Details**

This function is designed to be used in the field, although there are parts of it that are currently problematic. For example, in the field, there is typically no inkling of a responder or non-responder and yet the function as it currently stands is too wedded to the simulation scenario. Not hard to fix though.

**Value**

A vector of quantities is returned.

m0	number on control arm
m1	number on treatment arm
y0	number of responses in control
y1	number of responses in treatment
pi0Hat	estimate of the proportion of responders among control
pi1Hat	estimate of the proportion of responders among treatment
pi0HatH0	estimate of the proportion of responders among control under $H_0$
pi1HatH0	estimate of the proportion of responders among control under $H_0$
pi0HatH1	estimate of the proportion of responders among control under $H_1$
pi1HatH1	estimate of the proportion of responders among control under $H_1$
g1rRespH0	estimate of the generalized likelihood ratio statistic for response under $H_0$
g1rRespH1	estimate of the generalized likelihood ratio statistic for response under $H_1$
g1rSurvH0	estimate of the generalized likelihood ratio statistic for survival under $H_0$
g1rSurvH1	estimate of the generalized likelihood ratio statistic for survival under $H_1$
alphaHat	the estimate of $\alpha$
alphaHatH0	the estimate of $\alpha$ under $H_0$
alphaHatH1	the estimate of $\alpha$ under $H_1$
betaHat	the estimate of $\beta$
betaHatH0	the estimate of $\beta$ under $H_0$



```

sp23Design <- generateSP23Design(trueParameters, trialParameters)
d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                              nFU = trialParameters$followupTime,
                              pi0 = trueParameters$p0,
                              pi1 = trueParameters$p1,
                              theta = trueParameters$theta,
                              lambda0 = trueParameters$baselineLambda)
result <- executeSP23Design(sp23Design, d, trialParameters$interimLookTime[2])

## End(Not run)

```

---

exploreSP23Design      *Explore a specified design by simulation*

---

### Description

Explore a chosen design by generating simulated datasets and storing data from simulations for further analysis

### Usage

```
exploreSP23Design(sp23Design, numberOfSimulations = 25, rngSeed = 12345,
                 showProgress = TRUE)
```

### Arguments

sp23Design	A design object typically created by the function <a href="#">generateSP23Design</a>
numberOfSimulations	The number of simulations to use, default 25
rngSeed	A seed for the random number generator for reproducibility
showProgress	A flag (default TRUE) to show progress or not

### Details

This function is used while exploring the characteristics of a design. Results are accumulated and can be fed into analysis functions to inform choices.

### Value

A list of length `numberOfSimulations` where each entry is a data frame with number of interim looks rows and the following variables in the column.

m0	number on control arm
m1	number on treatment arm
y0	number of responses in control
y1	number of responses in treatment

$\pi_0\text{Hat}$	estimate of the proportion of responders among control
$\pi_1\text{Hat}$	estimate of the proportion of responders among treatment
$\pi_0\text{HatH}_0$	estimate of the proportion of responders among control under $H_0$
$\pi_1\text{HatH}_0$	estimate of the proportion of responders among control under $H_0$
$\pi_0\text{HatH}_1$	estimate of the proportion of responders among control under $H_1$
$\pi_1\text{HatH}_1$	estimate of the proportion of responders among control under $H_1$
$g_{lr}\text{RespH}_0$	estimate of the generalized likelihood ratio statistic for response under $H_0$
$g_{lr}\text{RespH}_1$	estimate of the generalized likelihood ratio statistic for response under $H_1$
$g_{lr}\text{SurvH}_0$	estimate of the generalized likelihood ratio statistic for survival under $H_0$
$g_{lr}\text{SurvH}_1$	estimate of the generalized likelihood ratio statistic for survival under $H_1$
$\alpha\text{Hat}$	the estimate of $\alpha$
$\alpha\text{HatH}_0$	the estimate of $\alpha$ under $H_0$
$\alpha\text{HatH}_1$	the estimate of $\alpha$ under $H_1$
$\beta\text{Hat}$	the estimate of $\beta$
$\beta\text{HatH}_0$	the estimate of $\beta$ under $H_0$
$\beta\text{HatH}_1$	the estimate of $\beta$ under $H_1$
$\gamma\text{Hat}$	the estimate of $\gamma$
$\gamma\text{HatH}_0$	the estimate of $\gamma$ under $H_0$
$\gamma\text{HatH}_1$	the estimate of $\gamma$ under $H_1$
$\text{hazard}$	the estimate of $d$
$v$	the estimate of $\Gamma_t$
$\text{rejectH}_0R$	a flag indicating if $H_0^R$ was rejected at the interim look
$\text{acceptH}_0R$	a flag indicating if $H_0^R$ was accepted (futility) at the interim look
$\text{rejectH}_0S$	a flag indicating if $H_0^S$ was rejected at the interim look
$\text{acceptH}_0S$	a flag indicating if $H_0^S$ was accepted (futility) at the interim look
$\text{b.metas.Last}$	the last Haybittle-Peto boundary for the survival end-point, if computed

### Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

### References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, 2011, (submitted).

**Examples**

```

## Not run:
trialParameters <- list(minimumNumberOfEvents = 20,
  minimumIncreaseInV = 0.2,
  numberRecruitedEachYear = c(80, 120, 160, 160),
  followupTime = 3,
  adminCensoringTime = 7,
  interimLookTime = c(1, 2, 3, 5, 7),
  type1ErrorForResponse = 0.05,
  type2ErrorForResponse = 0.01,
  glrBoundarySidedness = "one", # one sided or two-sided
  type1Error = 0.05,
  type2Error = 0.10,
  epsType1 = 1/3,
  epsType2 = 1/3)

## Case C of table 1 in paper
caseC.TrueParameters <- list(p0 = 0.3,
  p1 = 0.6,
  pdiffHyp=0.3,
  theta = list(
    alpha = 0,
    beta = 0,
    gamma = 0),
  baselineLambda = 0.35,
  etaHyp = 0.25)

## Do case C as example
sp23Design <- generateSP23Design(caseC.TrueParameters, trialParameters)
trialHistory <- exploreSP23Design(sp23Design, numberOfSimulations=25, rngSeed=2387487)

## End(Not run)

```

---

```
generateClinicalTrialData
```

*A function to generate some clinical trial data according the joint model of response and survival for simulations*

---

**Description**

The data is generated according to the model specified in the reference below, specifically,

$$\lambda(t | Y, Z) = \lambda_0(t) \exp(\alpha Y + \beta Z + \gamma Y Z)$$

**Usage**

```
generateClinicalTrialData(nRec, nFU, pi0, pi1, theta, lambda0, blockSize = 10)
```

**Arguments**

nRec	the number of patients recruited every year. Length(nRec) is the number of years of recruitment
nFUp	the number of additional years of followup
pi0	the probability of response under control arm
pi1	the probability of response under treatment arm
theta	the three dimensional parameter $(\alpha, \beta, \gamma)$ of the joint response/survival model
lambda0	the baseline hazard rate
blockSize	the size of the blocks for randomization of the treatment/control; we use block randomization

**Details**

Generates data from an exponential distribution according to the model and adhering to the recruitment goals for each calendar year

**Value**

A data frame consisting of the following variables.

entryTime	entry time of the patient into the trial
responseIndicator	an indicator of patient being a responder or not
treatmentIndicator	an indicator of patient being in treatment arm or control
timeToEvent	the time to event or death in the language of the paper

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

**Examples**

```
trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
```

```

                                type2Error = 0.10,
                                epsType1 = 1/3,
                                epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                      p1 = 0.3,
                      pdiffHyp=0.3,
                      theta = list(
                        alpha = 0,
                        beta = 0,
                        gamma = 0),
                      baselineLambda = 0.35,
                      etaHyp = 0.25)

rngSeed <- 9872831

d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                              nFUp = trialParameters$followupTime,
                              pi0 = trueParameters$p0,
                              pi1 = trueParameters$p1,
                              theta = trueParameters$theta,
                              lambda0 = trueParameters$baselineLambda)

```

---

generateInterimData     *Generate interim data for a clinical trial from a data set.*

---

### Description

Generate interim data at a given time from a dataset

### Usage

```
generateInterimData(clinicalTrialDF, interimTime, administrativeCensoringTime)
```

### Arguments

clinicalTrialDF

The data frame from which to generate the interim data. It is assumed that the variables entryTime, responseIndicator, treatmentIndicator and timeToEvent are present

interimTime     the interim time for which the data is to generated

administrativeCensoringTime

The administrative censoring time when the study concludes

### Details

As it stands this function also is geared towards the simulation scenario. Needs to be cleaned up a bit.





---

generateSP23Design	<i>Generate a seamless Phase II-III design object given some the true parameters and clinical trial parameters</i>
--------------------	--

---

### Description

Generate a seamless Phase II-III design object given some the true parameters and clinical trial parameters

### Usage

```
generateSP23Design(trueParameters, trialParameters)
```

### Arguments

**trueParameters** A list consisting of several components including  $p_0$ , the true probability of response under control,  $p_1$ , the true probability of response under treatment,  $\theta$ , a list of three items  $(\alpha, \beta, \gamma)$ ,  $\lambda$ , the base line hazard rate (constant for now),  $d$ , the hypothesized non-null hazard  $d$ .

**trialParameters**

A list consisting of several components including  $n$ , numberRecruitedEachYear, a vector of recruitment numbers for each year,  $t_1$ , interimLookTime, the calendar interim look times,  $t_2$ , followupTime, the follow-up time,  $t_3$ , adminCensoringTime, the administrative censoring time,  $glr$ , glrBoundarySidedness, either one or two-sided generalized likelihood ratio boundaries, default one-sided,  $\alpha$ , typeIError, the type I error desired,  $\beta$ , type2Error, the type II error desired, used only for computing futility boundaries (only nominally used; need to clarify),  $\gamma$ , epsTypeI, the fraction to spend in interim looks for the modified Haybittle-Peto boundaries,  $\delta$ , epsTypeII, the fraction to spend in interim looks for the modified Haybittle-Peto boundaries.

### Details

Generates a design object that is used throughout the simulation or an actual analysis.

### Value

An informal sp23Design object, a list of four items

**trueParameters** exactly the input above

**trialParameters**

exactly the input above

**glrBoundary** a matrix of dimension number of interim looks by 4, containing the boundaries for futility and efficacy for both response and survival

**interimLookHistoryDF**

A data frame as described in [exploreSP23Design](#).

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

**See Also**

[exploreSP23Design](#) and examples in the examples subdirectory of this package

**Examples**

```
## trial parameters in paper
trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
                        type2Error = 0.10,
                        epsType1 = 1/3,
                        epsType2 = 1/3)

## Case C of table 1 in paper
caseC.TrueParameters <- list(p0 = 0.3,
                              p1 = 0.6,
                              pdiffHyp=0.3,
                              theta = list(
                                alpha = 0,
                                beta = 0,
                                gamma = 0),
                              baselineLambda = 0.35,
                              etaHyp = 0.25)

## Do case C as example
sp23Design <- generateSP23Design(caseC.TrueParameters, trialParameters)
```

**Description**

A utility function to compute the hessian of the generalized (conditional) partial likelihood ratio statistic

**Usage**

```
hessian(theta, pi, interimData)
```

**Arguments**

theta	The three-element vector $(\alpha, \beta, \gamma)$
pi	The two-element vector $(\pi_0, \pi_1)$
interimData	The interim data frame

**Details**

Computes the hessian

**Value**

A  $3 \times 3$  matrix of the hessian

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik1

*Compute the response log-likelihood*

---

**Description**

Compute the response log-likelihood

**Usage**

```
loglik1(piVec, respSummary)
```

**Arguments**

piVec	The two-element vector of $(\pi_0, \pi_1)$
respSummary	A vector consisting of the summary of data described in <a href="#">computeResponseSummary</a>

**Details**

Computes the log-likelihood

**Value**

the log-likelihood

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik1GivenDelta	<i>Computes the constrained response log-likelihood (on the alternative)</i>
-------------------	--

---

**Description**

Computes the constrained response log-likelihood (on the alternative)

**Usage**

```
loglik1GivenDelta(p, respSummary, delta = 0)
```

**Arguments**

p	The probability $\pi_0$
respSummary	A vector consisting of the summary of data described in <a href="#">computeResponseSummary</a>
delta	The scalar value of the difference $\pi_1 - \pi_0$

**Details**

Computes the constrained response log-likelihood (on the alternative)

**Value**

the (constrained) response log likelihood

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik2                      *Computes the survival log-likelihood*

---

**Description**

Computes the survival log-likelihood

**Usage**

```
loglik2(theta, interimData)
```

**Arguments**

theta                      the three-element vector of  $(\alpha, \beta, \gamma)$   
interimData              The interim data

**Details**

Computes the survival log-likelihood

**Value**

the survival log-likelihood

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik2.repar0              *Computes the constrained survival log-likelihood*

---

**Description**

Computes the constrained survival log-likelihood

**Usage**

```
loglik2.repar0(xi, interimData, pi0, pi1, eta.hyp = 0)
```

**Arguments**

xi	the three-element vector of $(a = e^\alpha, b = e^\beta, c = e^\gamma)$
interimData	the interim data
pi0	the value $\pi_0$
pi1	the value $\pi_1$
eta.hyp	The hypothesised difference $d$ in the alternative hypothesis

**Details**

This uses the reparametrization above in terms of  $(a, b, c)$  rather than  $(\alpha, \beta, \gamma)$

**Value**

The constrained survival log-likelihood

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

---

mHP.b

*Compute the modified Haybittle-Peto boundary*

---

**Description**

Compute the modified Haybittle-Peto boundary

**Usage**

```
mHP.b(mu = c(0, 0), v = c(1, 2), alpha = 0.05, eps = 1/2, side = c("one", "two"))
```

**Arguments**

mu	The mean vector
v	The variance vector, usually proportional to information in calendar time
alpha	The significance desired
eps	The fraction of alpha to use
side	one-sided or two-sided (one or two)

**Details**

Compute the modified Haybittle-Peto boundary

**Value**

the modified Haybittle-Peto boundary

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

 mHP.c

---

*Compute the modified Haybittle-Peto boundary for the final look*


---

**Description**

Compute the modified Haybittle-Peto boundary for the final look

**Usage**

```
mHP.c(mu = c(0, 0, 0), v = c(1, 2, 3), b = 3, alpha = 0.05,
      eps = 1/2, side = c("one", "two"))
```

**Arguments**

mu	the mean vector
v	The variance vector, usually proportional to information in calendar time
b	The (constant) modified Haybittle-Peto boundary, typically computed by <a href="#">mHP.b</a>
alpha	The significance level desired
eps	The fraction of alpha to use
side	one-sided or two-sided (one or two)

**Details**

Compute the modified Haybittle-Peto boundary for the final look

**Value**

the modified Haybittle-Peto boundary for the final look

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

performInterimLook      *Perform an interim look in a seamless Phase II-III clinical trial*

---

**Description**

Perform an interim look in a seamless Phase II-III clinical trial

**Usage**

```
performInterimLook(k, trueParameters, trialParameters, glrBoundary,
                  interimData, interimLookHistoryDF, argRejectH0R)
```

**Arguments**

k	the index of the look
trueParameters	the true parameters, usually available in an object generated by <a href="#">generateSP23Design</a>
trialParameters	the trial parameters, usually available in an object generated by <a href="#">generateSP23Design</a>
glrBoundary	the generalized likelihood ratio boundaries, usually available in an object produced by <a href="#">generateSP23Design</a>
interimData	the interim data
interimLookHistoryDF	the interim look history data frame matrix described in <a href="#">exploreSP23Design</a>
argRejectH0R	A flag that indicates whether $H_0^R$ has been rejected in the previous look; A value of FALSE is used for first look.

**Details**

Perform an interim look in a seamless Phase II-III clinical trial

**Value**

a vector of named values described in [exploreSP23Design](#), essentially providing a new row to the interim look history data frame

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.



**Examples**

```

trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
                        type2Error = 0.10,
                        epsType1 = 1/3,
                        epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                       p1 = 0.3,
                       pdiffHyp=0.3,
                       theta = list(
                           alpha = 0,
                           beta = 0,
                           gamma = 0),
                       baselineLambda = 0.35,
                       etaHyp = 0.25)

rngSeed <- 9872831

sp23Design <- generateSP23Design(trueParameters, trialParameters)
d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                              nFU = trialParameters$followupTime,
                              pi0 = trueParameters$p0,
                              pi1 = trueParameters$p1,
                              theta = trueParameters$theta,
                              lambda0 = trueParameters$baselineLambda)
dInterim <- generateInterimData(d, trialParameters$interimLookTime[1],
                               trialParameters$adminCensoringTime)
dInterim <- dInterim[order(dInterim$timeToEvent), ]
## This is a tricky function to use for all but the first interim look;
## see executeSP23Design code for details! Reason: interim look k depends
## on results of interim look k-1
##
performInterimLook(1, sp23Design$trueParameters, trialParameters, sp23Design$glrBoundary,
                  dInterim, sp23Design$interimLookHistoryDF,
                  argRejectH0R = FALSE)

```

---

resetSP23Design

*Reset the design object so that counts and results are zeroed out*


---

**Description**

Reset the design object so that counts and results are zeroed out

**Usage**

```
resetSP23Design(sp23Design)
```

**Arguments**

sp23Design      An object usually the result of [generateSP23Design](#)

**Details**

Reset the design object so that counts and results are zeroed out

**Value**

A new sp23Design object with counts and results zeroed out

**Author(s)**

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

**References**

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

**Examples**

```
## Not run:
trialParameters <- list(minimumNumberOfEvents = 20,
  minimumIncreaseInV = 0.2,
  numberRecruitedEachYear = c(80, 120, 160, 160),
  followupTime = 3,
  adminCensoringTime = 7,
  interimLookTime = c(1, 2, 3, 5, 7),
  type1ErrorForResponse = 0.05,
  type2ErrorForResponse = 0.01,
  glrBoundarySidedness = "one", # one sided or two-sided
  type1Error = 0.05,
  type2Error = 0.10,
  epsType1 = 1/3,
  epsType2 = 1/3)

## Case C of table 1 in paper
caseC.TrueParameters <- list(p0 = 0.3,
  p1 = 0.6,
  pdiffHyp=0.3,
  theta = list(
    alpha = 0,
    beta = 0,
    gamma = 0),
  baselineLambda = 0.35,
  etaHyp = 0.25)
```

```

## Do case C as example
sp23Design <- generateSP23Design(caseC.TrueParameters, trialParameters)
## do something ...
sp23Design <- resetSP23Design(sp23Design)

## End(Not run)

```

---

solveForCGivenABD      *A convenience function to reduce dimension by solving for one variable  $c$  in terms of others  $a, b, d$*

---

### Description

A convenience function to reduce dimension by solving for one variable  $c$  in terms of others  $a, b, d$

### Usage

```
solveForCGivenABD(piVec, a, b, d)
```

### Arguments

piVec	The two-element vector of $(\pi_0, \pi_1)$
a	The value for $a$
b	The value for $b$
d	The value for $d$

### Details

Just solves the equation in closed form

### Value

the value for  $c$

### Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

### References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, *Statistics in Medicine*, Volume 31, issue 18, p.1944-1960, 2012.

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