Package 'OptInterim'

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Type Package

Title Optimal Two and Three Stage Designs for Single-Arm and Two-Arm Randomized Controlled Trials with a Long-Term Binary Endpoint

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Description Optimal two and three stage designs monitoring time-to-event endpoints at a specified timepoint

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`OptInterim-package` *Optimal Two and Three Stage Designs with Time-to-event Endpoints Evaluated at a Pre-specified Time.*

Description

`OptimDes` is the primary function in the package `OptInterim`. Detailed documentation of the design and a package vignette with examples can be found under "directory" on the package HTML help page. The user supplies the projected accrual distribution and distributions for time to event under the null and alternative hypotheses. `OptimDes` returns the total sample size, the interim time and sample size, and boundaries for decision rules.

`plot.OptimDes` can be applied to the output of `OptimDes` to evaluate other two-stage or three-stage designs that may achieve near optimal results for both of the implemented optimality criteria. `print.OptimDes` produces a summary of the design with a comparison to a standard single-stage design (which can also be obtained from `FixDes`) Design parameters for nearly optimal designs can be evaluated with `np.OptimDes`. Statistical tests for a two-stage or three-stage design are implemented in `TestStage`.

The function `SimDes` produces simulations under the assumed design by default to check the accuracy of asymptotic approximations. By supplying alterative accrual and survival distributions, the performance of the design and estimation can be checked for robustness.

The function `weibPmatch` can be used to find parameters of a Weibull distribution that match a event-free rate at a specified time. Function `weibull.plot` displays a null-alternative pair of hypothesized Weibull survival functions.

Details

Package:	OptInterim
Type:	Package
Version:	3.0
Date:	2012-12-03
License:	GPL version 2 or later

Author(s)

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See Also

`Package Survival`

`FixDes` *Construct a Single-stage Design for a time-to-event Endpoint Evaluated at a Pre-specifed Time Versus Either a Known Standard Control or a Randomized Comparative Control*

Description

Find the sample size, duration of accrual, and test boundary for a single-stage design with an event-free endpoint versus either a known standard control or a randomized comparative control. Testing is one-sided based on the Kaplan-Meier estimator evaluated at a user-specified time point.

Usage

```
FixDes(B.init, m.init, alpha, beta, param, x, num.arm, r=0.5)
```

Arguments

`B.init`	A vector of user-specified time points (B1, ..., Bb) that determine a set of time intervals with uniform accrual.
`m.init`	The projected number of patients that can be accrued within the time intervals determined by `B.init`.
`alpha`	Type I error.
`beta`	Type II error.
`param`	Events should be defined as poor outcomes (e.g. death, progression). Computations and reporting are based on the proportion without an event at a pre-specified time, `x`. For constructing an optimal design, complete event-free distributions at all times must be specified for the control condition (Null), and for the alternative "effective" treatment. Weibull distributions are currently implemented. `param` is a vector of length 4: (shape null, scale null, shape alternative, scale alternative). The R parameterization of the Weibull distribution is used.
`x`	Pre-specified time for the event-free endpoint (e.g., 1 year).
`num.arm`	Number of treatment arms. `num.arm`=1 for single-arm trial assuming a known standard control. `num.arm`=2 for two-arm randomized trial with a comparative control arm.
`r`	Proportion of patients randomized to the treatment arm. By default, `r`=0.5.

Details

Estimation is based on the Kaplan-Meier or Nelson-Aalen estimators evaluated at a target time (e.g., 1 year). The event-free rates at the target time are computed from Weibull distributions assumed for the treatment and control distributions, as is done in function `OptimDes`. The design depends only on the event-free rates at the target time (except for small changes due to rounding with different survival functions). The duration of accrual depends on the projected maximum accrual rates.

Value

A list with components:

n0	Fixed design sample size.
DA	Duration of accrual.
SL	Total study length (time, DA+x).
n0E	n0 based on exact binomial test.
DAE	DA based on exact binomial test.
SLE	SL based on exact binomial test.
C	Rejection cutpoint for the test statistic.

Note

The single-stage sample size is used as the starting value for evaluating the optimal n for a two-stage design in OptimDes.

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References

Huang B., Talukder E. and Thomas N. Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2(1)**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

OptimDes, TestStage, SimDes

Examples

```
B.init <- c(1, 2, 3, 4, 5)
m.init <- c(15, 20, 25, 20, 15)
alpha <- 0.05
beta <- 0.1
param <- c(1, 1.09, 2, 1.40)
x <- 1

# H0: S0=0.40 H1: S1=0.60

FixDes(B.init, m.init, alpha, beta, param, x,num.arm=1)
```

```
m.init <- 5*c(15, 20, 25, 20, 15)
FixDes(B.init, m.init, alpha, beta, param, x,num.arm=2)
```

`np.OptimDes` *Optimal Two-Stage or Three-Stage Designs with User-specified Combined Sample Size or Study Length*

Description

Construct a two-stage or three-stage design with a time-to-event endpoint evaluated at a pre-specified time (e.g., 6-month progression-free survival) comparing treatment versus either a historical control rate with possible stopping for futility (single-arm), or an active control arm with possible stopping for both futility and superiority (two-arm), after the end of Stage 1 utilizing time to event data. The design minimizes either the expected duration of accrual (EDA), the expected sample size (ES), or the expected total study length (ETSL). The maximum combined sample size for both stages is pre-specifed by the user.

Usage

```
np.OptimDes(
            B.init, m.init, alpha, beta, param, x, n = NULL, pn = NULL,
         pt = NULL, target = c("EDA", "ETSL","ES"), sf=c("futility","OF","Pocock"),
           num.arm,r=0.5,num.stage=2,pause=0,
           control = OptimDesControl(), ...)
```

Arguments

`B.init`	A vector of user-specified time points (B1, ..., Bb) that determine a set of time intervals with uniform accrual.
`m.init`	The projected number of patients that can be accrued within the time intervals determined by `B.init`.
`alpha`	Type I error.
`beta`	Type II error.
`param`	Events should be defined as poor outcomes (e.g. death, progression). Computations and reporting are based on the proportion without an event at a pre-specified time, `x`. For constructing an optimal design, complete event-free distributions at all times must be specified for the control condition (Null), and for the alternative "effective" treatment. Weibull distributions are currently implemented. `param` is a vector of length 4: (shape null, scale null, shape alternative, scale alternative). The R parameterization of the Weibull distribution is used.
`x`	Pre-specified time for the event-free endpoint (e.g., 1 year).
`n`	User-specified combined sample size for both stages.

pn	Combined sample size for both stages specified by the ratio of the targetted two-stage sample size to the correponding sample size for a single-stage design.
pt	Combined sample size for both stages specified by the ratio of the targetted two-stage study length to the correponding study length for a single-stage design.
target	The expected duration of accrual (EDA) is minimized with target="EDA", the expected total study length is minimized with target="ETSL", and the expected sample size with target="ES".
sf	Spending function for alpha at the end of Stage 1. There are three types of spending functions: no efficacy stopping with sf="futility", O'Brien-Fleming boundaries with sf="OF", and Pocock boundaries with sf="Pocock".
num.arm	Number of arms: a single-arm design with num.arm=1, or a randomized two-arm design with num.arm=2.
r	Proportion of patients randomized to the treatment arm when num.arm=2. By default, r=0.5.
num.stage	Number of stages: a two-stage design with num.stage=2, or a three-stage design with num.stage=3.
pause	The pause in accrual following the scheduled times for interim analyses. Data collected during the pause on the previously accrued patients are included in the interim analysis conducted at the end of the pause. Accrual resumes after the pause without interuption as if no pause had occurred. Default is pause=0.
control	An optional list of control settings. See OptimDesControl for the parameters that can be set and their default values.
...	No additional optional parameters are currently implemented

Details

Plots (plot.OptimDes) based on the ouput of OptimDes can be used to find compromise designs based on different combined sample sizes with near optimal values for both ETSL ES, and EDA. np.OptimDes can be used to compute ETSL, ES, EDA, and the other design parameters for any specified total sample size.

The targeted combined sample size must be specified by one of three equivalent approaches: n, pn, and pt. The design calculations assume Weibull distributions for the event-free endpoint in the treatment group, and for the (assumed known, "Null") control distribution.

The function weibPmatch can be used to select Weibull parameters that yield a target event-free rate at a specified time.

Value

A list of class OptimDes with the same output as function OptimDes.

Author(s)

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References

Huang B., Talukder E. and Thomas N. (2010). Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

OptimDes, plot.OptimDes, weibPmatch

Examples

```
## Not run:
B.init <- c(1, 2, 3, 4, 5)
m.init <- c(15, 20, 25, 20, 15)
alpha <- 0.05
beta <- 0.1
param <- c(1, 1.09, 2, 1.40)
x <- 1

# H0: S0=0.40 H1: S1=0.60

object14 <- np.OptimDes(B.init,m.init,alpha,beta,param,x,pt=1.1,target="ETSL",sf="futility",num.arm=1,num.stage

## End(Not run)
```

`OptimDes` *Construct Optimal Two-stage or Three-stage Designs with Time-to-event Endpoints Evaluated at a Pre-specified Time*

Description

Construct an optimal two-stage or three-stage designs with a time-to-event endpoint evaluated at a pre-specified time (e.g., 6 months) comparing treatment versus either a historical control rate with possible stopping for futility (single-arm), or an active control arm with possible stopping for both futility and superiority (two-arm), after the end of Stage I utilizing time to event data. The design minimizes either the expected duration of accrual (EDA), expected sample size (ES), or the expected total study length (ETSL).

Usage

```
OptimDes(
B.init, m.init, alpha, beta, param, x, target = c("EDA", "ETSL","ES"),
sf=c("futility","OF","Pocock"), num.arm,r=0.5, num.stage=2,
pause=0,
control = OptimDesControl(),...)
```

Arguments

B.init	A vector of user-specified time points (B1, ..., Bb) that determine a set of time intervals with uniform accrual.
m.init	The projected number of patients that can be accrued within the time intervals determined by B.init. A large number of potential patients results in long execution times for OptimDes, so unrealistically large values should not be entered.
alpha	Type I error.
beta	Type II error.
param	Events should be defined as poor outcomes (e.g. death, progression). Computations and reporting are based on the proportion without an event at a pre-specified time, x. For constructing an optimal design, complete event-free distributions at all times must be specified for the control condition (Null), and for the alternative "effective" treatment. Weibull distributions are currently implemented. param is a vector of length 4: (shape null, scale null, shape alternative, scale alternative). The R parameterization of the Weibull distribution is used.
x	Pre-specified time for the event-free endpoint (e.g., 1 year).
target	The expected duration of accrual (EDA) is minimized with target="EDA", the expected total study length is minimized with target="ETSL", or the expected sample size with target="ES".
sf	Spending function for alpha at the end of Stage 1. There are three types of spending functions: no efficacy stopping with sf="futility", O'Brien-Fleming boundaries with sf="OF", and Pocock boundaries with sf="Pocock".
num.arm	Number of arms: a single-arm design with num.arm=1, or a randomized two-arm design with num.arm=2.
r	Proportion of patients randomized to the treatment arm when num.arm=2. By default, r=0.5.
num.stage	Number of stages: a two-stage design with num.stage=2, or a three-stage design with num.stage=3.
pause	The pause in accrual following the scheduled times for interim analyses. Data collected during the pause on the previously accrued patients are included in the interim analysis conducted at the end of the pause. Accrual resumes after the pause without interuption as if no pause had occurred. Default is pause=0.
control	An optional list of control settings. See OptimDesControl. for the parameters that can be set and their default values.
...	No additional optional parameters are currently implemented.

Details

OptimDes finds an two-stage or three-stage design with a time to event endpoint evaluated at a pre-specified time with potential stopping after the first stage.

For single arm designs, it implements the Case and Morgan (2003) and Huang, Talukder and Thomas (2010) generalizaton of the Simon (1989) two-stage design for comparing a treatment to a known standard rate with possible stopping for futility at the interim.

For randomized two-arm comparative designs, it allows an early stopping for both futility and superiority. The spending function for superiority can be chosen with argument sf.

The design minimizes either the expected duration of accrual (EDA), expected sample size (ES), or the expected total study length (ETSL).

The design calculations assume Weibull distributions for the event-free endpoint in the treatment group, and for the (assumed known, "Null") control distribution. The function weibPmatch can be used to select Weibull parameters that yield a target event-free rate at a specified time. Estimation is based on the Kaplan-Meier or Nelson-Aalen estimators evaluated at a target time (e.g., 1 year). The full treatment and control distributions and the accrual distribution affect power (and alpha level in some settings), see Case and Morgan (2003)).

Accrual rates are specified by the user. These rates can differ across time intervals specified by the user (this generalizes the results in Case and Morgan).

A package vignette as user manual can be found in the /doc subdirectory of the OptInterim package. It can be accessed from the HTML help page for the package.

Value

A list with components:

target	The optimizaton target ("EDA" or "ETSL" or "ES").
sf	The alpha spending function ("futility" or "OF" or "Pocock").
test	A vector giving the type I error alpha, type II error beta, Weibull parameters param and survival time of interest x.
design	A vector giving the number of study arms num.arm, treatment randomization rate r, the number of study stages num.stage, the pause in accrual before an interim analysis pause.
accrual	A list containing the input vectors B.init and m.init.
result	A 5-element vector containing the expected duration of accrual (EDA), the expected total study length (ETSL), the expected sample size of the optimal design (ES), and the probability of stopping under the Null (pstopNULL) and Alternative hypotheses (pstopAlt).
n	A two (or three)-element vector containing the sample size for the interim analysis and the sample size if all stages are completed.
stageTime	A 3 (or 4)-element vector giving the times for the interim and final analyses, and maximum duration of accrual. Interim times are given for the beginning of any pause before the analysis occurs.
boundary	A vector giving the rejection cutpoints (see Test2stage) for the test statistic and decision rules.

se	A vector of length 4 (or 6) with the asymptotic standard errors at the iterim and final analysis under the null hypothesis, followed by the corresponding SEs under the alternative hypothesis. These SEs must be divided by the square root of sample size.
u	A two (or three)-element vector giving means of interim test statistics under H1. See detailed description. It is also used to compute conditional power.
exposure	The expected total exposure of patients at the time of the planned interim analysis (including any accrual pause). Patient exposure is truncated by both the interim analysis time (including any pause) and the target surival time (i.e., no exposure after x). Exposure is a vector of length 1 or 2. The first value is the expected exposure at the first interim analysis. For two-stage, single-group designs, the second value is exposure with the Case-Morgan finite sample adjustment. For 3-stage designs, the second value is the exposure at the second interim analysis. For two-stage, two-group designs, exposure is a scalar indicating the expected exposure at the first interim analysis.
all.info	A data frame containing the results for all of the evaluated sample sizes.
single.stage	A six-element vector giving the sample size fix.n, duration of accrual DA, study length SL, and corresponding values based on the exact binomial test for a one-arm single-stage design and the Fisher exact test for a two-arm single-stage design with the design distributional assumptions.

Note

The algorithm will search for the optimal n between the sample size for a single-stage design and the user specified maximum sample size sum(m.init).

When the length of B.init or m.init is 1, the accrual rate is constant as in Lin et al. (1996), Case and Morgan (2003).

Author(s)

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References

Huang B., Talukder E. and Thomas N. (2010). Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2**, 51–61.

Case M. D. and Morgan T. M. (2003). Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996). Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989). Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

np.OptimDes, print.OptimDes, plot.OptimDes, weibPmatch

Examples

```
## Not run:
B.init <- c(1, 2, 3, 4, 5)
m.init <- c(15, 20, 25, 20, 15)
alpha <- 0.05
beta <- 0.1
param <- c(1, 1.09, 2, 1.40)
x <- 1

# H0: S0=0.40 H1: S1=0.60

object12 <- OptimDes(B.init,m.init,alpha,beta,param,x,target="EDA",
sf="futility",num.arm=1,num.stage=2,control=OptimDesControl(n.int=c(1,5),trace=TRUE))
print(object12)


m.init <- 4*c(15, 20, 25, 20, 15)
object2 <- OptimDes(B.init,m.init,alpha,beta,param,x,target="EDA",sf="futility",num.arm=2)
print(object2)

object23O <- OptimDes(B.init,m.init,alpha,beta,param,x,target="ETSL",sf="OF",
num.arm=2,num.stage=3,control=OptimDesControl(trace=TRUE,aboveMin=c(1.05,1.10)))
print(object3)

## End(Not run)
```

`OptimDesControl` *Set parameters controlling numerical methods for OptimDes and np.OptimDes*

Description

Set parameters controlling numerical methods for `OptimDes` and `np.OptimDes`

Usage

```
OptimDesControl(trace=TRUE,tol=0.01,n.int=c(1,5),aboveMin=c(1.05,1.10))
```

Arguments

`trace`	A logical value indicating if a trace of the iteration progress should be printed. Default is `FALSE`. If `TRUE` the sample size `n`, the corresponding optimal correlation `rho` and minimized `EDA(ETSL)` are printed at the conclusion of each iteration.
`tol`	`tol` is the desired accuracy for `optimize`. Default is 0.01.
`n.int`	A two-element vector containing the grid search interval for maximum sample size of one-arm and two-arm designs. Default is c(1, 5).

aboveMin	The minimization method searches by increasing order from the single-stage sample size until the criteria exceeds the current minimum by a multiplicative factor of aboveMin. The search will also terminate if sum(m.init) is reached. Default is 1.05 for one-arm, 1.10 for two-arm designs.

Author(s)

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References

Huang B., Talukder E. and Thomas N. Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2(1)**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

OptimDes, np.OptimDes

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plot.OptimDes — *Plot efficiency of optimal two-stage or three-stage designs as a function of the total sample size or study length*

Description

Output from function OptimDes is used to display the ETSL, ES and EDA for a two-stage or three-stage design relative to a single-stage design as a function of the combined-stage sample size or study length.

Usage

```
## S3 method for class 'OptimDes'
plot(x, xscale = "t", l.type = 1:5, l.col =
c("blue", "green", "purple", "red", "dark red"), CMadj=F,...)
```

Arguments

x	Output from function OptimDes.
xscale	Scale of the x-axis. "t" for combined-stage study length. "n" for combined sample size. Default is t.
l.type	Line types for the plot. Default is 1-5.

l.col	Line colors for the plot. Default is "blue" for ETSL, "green" for EDA, "purple" for ES, "red" for t1 and "dark red" for t2 if it's a three-stage design.
CMadj	If true, the sample sizes and times are adjusted by the ratio of the exact binomial to asymptotic normal sample size for the single stage design, as in Case and Morgan (2003). Proportional adjustment of times and sample sizes are made even if the accrual rates are not constant. This adjustment is valid for two-stage 1-group designs. Default is false.
...	Additional graphical parameters passed to function plot.

Details

The plot displays the tradeoff between ETSL, EDA and ES as a function of the combined sample size or study length. Robustness of the optimal design to deviations from the target sample size can be explored. The plots often suggest compromised designs achieving near-optimal results for both EDA and ETSL may be a better choice. Test boundary values (C1L, C1U, etc), and numerical values of other design parameters, can be obtained for a design selected from the plots using function np.OptimDes.

The plot also includes the times of the interim analysis (t1, t1) as a ratio to the time for a corresponding single-stage analysis.

Author(s)

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References

Huang B., Talukder E. and Thomas N. Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2(1)**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

print.OptimDes, OptimDes, np.OptimDes

`print.OptimDes` *Print Objects Output By OptimDes*

Description

Print an object output by `OptimDes`.

Usage

```
## S3 method for class 'OptimDes'
print(x, dig = 3, all=FALSE, condPow=F,
                      CMadj=F, ...)
```

Arguments

`x`	Object output by `OptimDes`.
`dig`	Number of digits printed.
`all`	If `TRUE`, results are printed for all total sample sizes evaluated by `OptimDes`.
`condPow`	The conditional probability of rejecting the null hypothesis computed assuming the alternative distributions and an interim Z statistic equal to the interim test boundary `C1` is reported when `condPow=T`.
`CMadj`	If true, the sample sizes and times are adjusted by the ratio of the exact binomial to asymptotic normal sample size for the single stage design, as in Case and Morgan (2003). Proportional adjustments of times and sample sizes are made even if the accrual rates are not constant. Default is false.
`...`	Optional print arguments, see `print.default`.

Author(s)

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References

Huang B., Talukder E. and Thomas N. Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2(1)**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

`plot.OptimDes`, `OptimDes`

SimDes *Simulation Studies for Two-Stage or Three-Stage Designs from function OptimDes*

Description

Simulation experiments to compare the alpha level, power and other features of two-stage or three-stage designs from function OptimDes with the targetted values.

Usage

```
SimDes(object,B.init,m.init,weib0,weib1,interimRule='e1',
       sim.n=1000,e1conv=1/365,CMadj=F,attainI=1,attainT=1,FixDes="F",
       Rseed)
```

Arguments

object	Output object of function OptimDes.
B.init	A vector of user-specified time points (B1, ..., Bb) that determine a set of time intervals with uniform accrual. This vector needs to be specified only if its values differ from the call to OptimDes.
m.init	The projected number of patients that can be accrued within the time intervals determined by B.init. This vector needs to be specified only if its values differ from the call to OptimDes.
weib0	A vector with the shape and scale for the Weibull distribution under the null hypothesis. These need to be specified only if they differ from the input to OptimDes.
weib1	A vector with the shape and scale for the Weibull distribution under the alternative hypothesis. These need to be specified only if they differ from the input to OptimDes.
interimRule	The interim analysis is performed when the planned n1 patients are accrued regardless of the time required when interimRule='n1'. The interim analysis is performed at the planned time t1 regardless of the number of patients accrued when interimRule='t1'. The interim analysis is performed when the truncated (by x) total exposure matches the total expected exposure when interimRule='e1'. The default is 'e1'.
sim.n	The number of simulation replications.
e1conv	Convergence criteria for matching the truncated exposure when interimRule='e1'. The default is 1/365, which is appropriate provided B.init is specified in years
CMadj	If true, the n, n1, and t1 are adjusted by the ratio of the exact binomial to asymptotic normal sample size for the single stage design, as in Case and Morgan (2003). Proportional adjustment of times and sample sizes are made even if the accrual rates are not constant. The adjustment to the mda is made through the adjustment to n rather than by multiplication to ensure consistency with accrual boundaries. The truncated exposure time is matched to the adjusted time of the interim analysis. Default is false.

attainI	Samples sizes and times of the interim analyses often differ from the exact targetted values for operational reasons. The attainI permits simulations with a different interim time or sample size (depending on interimRule) by a specified fraction.
attainT	Simulations with a total sample size (assuming the trial does not stop based on the interim analysis) that differs from the planned total by a specified fraction.
FixDes	If FixDes="E" or "N", a fixed design is simulated with the sample size determined by the Exact or Normal approximation. All other options for modifying the simuations are ignored. The alpha level and power based on an exact test and the normal approximation are returned. All other output variables are 0. The default is "F"
Rseed	Optional integer for input to function set.seed. If unspecified, the random seed status at the time of the function call is used.

Details

sim.n(default is 1000) simulation experiments are conducted to assess how close the empirical type I and II error rates come to the target values.

Simulation studies can also be used to assess the performance of the optimal design under misspecification of the design parameters. For example, if the Weibull shape and scale parameters of the time to event distributions are changed, or if the accrual rates are changed. (see Case and Morgan, 2003, for discussion of this topic).

The function weibPmatch can be used to select Weibull parameters that yield a target event-free rate at a specified time.

Value

A vector with:

alphaExact	Estimated alpha level using an exact test for the final test. It is NA if the design allows interim stopping for superiority.
alphaNorm	Estimated alpha level using approximately normal tests.
powerExact	Estimated power using an exact test for the final test. It is NA if the design allows interim stopping for superiority.
powerNorm	Estimated power using approximately normal tests.
eda	Estimated mean duration of accrual under the null hypothesis.
etsl	Estimated mean total study length under the null hypothesis.
es	Estimated mean total sample size under the null hypothesis.
edaAlt	Estimated mean duration of accrual under the alternative hypothesis.
etslAlt	Estimated mean total study length under the alternative hypothesis.
esAlt	Estimated mean total sample size under the alternative hypothesis.
pstopNull	The proportion of trials stopped for futility at the interim analysis under the null hypothesis.
pstopAlt	The proportion of trials stopped for futility at the interim analysis under the alternative hypothesis.

pstopENull	The proportion of trials stopped for efficacy at the interim analysis under the null hypothesis.
pstopEAlt	The proportion of trials stopped for efficacy at the interim analysis under the alternative hypothesis.
aveE	Average total (truncated at x) exposure at time of interim analysis.
pinfoNull	The proportion of the total information obtained at the interim analysis under the null hypothesis.
pinfoNull2	The proportion of the total information obtained at the second interim analysis under the null hypothesis when num.stage=3.
pinfoAlt	The proportion of the total information obtained at the interim analysis under the alternative hypothesis.
n1	Average sample size at interim.
n2	Average sample size at second interim.
t1	Average time at interim.
t2	Average time at second interim.
difIntSupL	Lowest interim survival rate difference stopped for efficacy.
difIintSupH	Highest interim survival rate difference not stopped for efficacy.
difIntFutL	Lowest interim survival rate difference continued to final analysis based on the normal approximation.
difIntFutH	Highest interim survival rate difference resulting in futility terimination based on the normal approximation.
difFinSupL	Lowest final survival rate difference rejecting null based on the normal approximation.
difFinFutH	Highest final survival rate difference without rejecting null based on the normal approximation.

Author(s)

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References

Huang B., Talukder E. and Thomas N. Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2(1)**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

OptimDes, TestStage, weibPmatch

Examples

```
## Not run:
B.init <- c(1, 2, 3, 4, 5)
m.init <- c(15, 20, 25, 20, 15)
alpha <- 0.05
beta <- 0.1
param <- c(1, 1.09, 2, 1.40)
x <- 1

# H0: S0=0.40 H1: S1=0.60

object1 <- OptimDes(B.init,m.init,alpha,beta,param,x,target="EDA",sf="futility",num.arm=1)

SimDes(object1,sim.n=100)

### Stopping based on pre=planned time of analysis
SimDes(object1,interimRule='t1',sim.n=100)

### accrual rates differ from planned
SimDes(object1,m.init=c(5,5,25,25,25),sim.n=100)

## End(Not run)
```

`TestStage` *Statistical test for two-stage or three-stage designs from function OptimDes*

Description

This function performs the hypothesis tests for the two-stage or three-stage designs with event-free endpoint from `OptimDes`.

Usage

```
TestStage(tan,tstage,x,num.arm,num.stage,
          Y1,T1,Y0=NULL,T0=NULL,p0=NULL,
          C1L=NULL,C1U=NULL,C2L=NULL,C2U=NULL,C3U=NULL,
          printTest=TRUE,
          cen1=rep(1,length(T1)),cen0=rep(1,length(T0)))
```

Arguments

`tan`	Study time (from first accrual) of the analysis.
`tstage`	`tstage=1` for the first interim analysis. `tstage=2` for the second analysis interim analysis when `num.stage=3`, or the final analysis when `num.stage=2`. `tstage=3` for the final analysis when `num.stage=3`.
`x`	Pre-specified time for the event-free endpoint (e.g., 1 year).

num.arm	Number of treatment arms. num.arm=1 for single-arm trial and num.arm=2 for a two-arm randomized trial.
num.stage	Number of trial stages: num.stage=2 or num.stage=3.
Y1	A vector containing the study start times (measured from the beginning of the study) of patients in the treatment arm. If times occuring after the analysis time tan are included, they are appropriately censored.
T1	A vector containing the event times corresponding to Y1.
Y0	A vector containing the study start times (measured from the beginning of the study) of patients in the control arm. It does not need to be set for 1-arm trials. If times occuring after the analysis time tan are included, they are appropriately censored.
T0	A vector containing the event times corresponding to Y0.
p0	The event rate under the null hypothesis.
C1L	The study is terminated for futility after the first stage if the Z-statistic is <=C1.
C1U	The study is terminated for efficacy after the first stage if the Z-statistic is >=C1U.
C2L	For a three-stage design, stop for futility after the second stage if Z<=C2.
C2U	For a three-stage design, stop for efficacy after the second stage if the Z>=C2U. For a two-stage design, reject the null hypothesis at the final stage if the Z>=C2U.
C3U	For a three-stage design, reject the null hypothesis at the final stage if the Z>=C3U.
printTest	If TRUE (default), the result of the test and the interim decision is printed.
cen1	The times in T1 are regarded as events unless they are set to censored by setting the corresponding value in cen1 to zero.
cen0	The times in T0 are regarded as events unless they are set to censored by setting the corresponding value in cen0 to zero.

Details

The hypothesis tests are performed in two stages as described in Huang, Talukder and Thomas (2010) and Case and Morgan (2003) for single-arm designs, and extended to the randomized two-arm two-stage and three-stage designs.

For two-stage designs:

Stage 1. Accrue patients between time 0 and time t1. Each patient will be followed until failure, or for x years or until time t1, whichever is less. Calculate the normalized interim test statistic Z1. If Z1<=C1, stop the study for futility; For randomized two-arm trials, if Z1>=C1U, stop the study for efficacy; otherwise, continue to the next stage.

Stage 2. Accrue patients between t1 and MDA. Follow all patients until failure or for x years, then calculate the normalized final test statistic Z2, and reject H0 if Z2>=C2.

For three-stage designs:

Stage 1. Accrue patients between time 0 and time t1. Each patient will be followed until failure, or for x years or until time t1, whichever is less. Calculate the normalized interim test statistic Z1. If Z1<=C1, stop the study for futility; For randomized two-arm trials, if Z1>=C1U, stop the study for efficacy; otherwise, continue to the next stage.

Stage 2. Accrue patients between t1 and t2. Follow all patients until failure or for x years, then calculate the normalized final test statistic Z2. If Z2<=C2, stop the study for futility; For randomized two-arm trials, if Z2>=C2U, stop the study for efficacy; otherwise, continue to the next stage.

Stage 3. Accrue patients between t2 and MDA. Follow all patients until failure or for x years, then calculate the normalized final test statistic Z3, and reject H0 if Z3>=C3.

The test statistic is based on the Nelson-Aalen estimator of the cumulative hazard function.

Value

A vector containing results for the interim analysis or the final analysis:

z	The test statistic
se	Standard error of sum of the cummulative hazards (not log cummulative hazards) at time x.
cumL	A two-element vector of cummulative hazard estimators at time x.

Author(s)

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References

Huang B., Talukder E. and Thomas N. Optimal two-stage Phase II designs with long-term endpoints. *Statistics in Biopharmaceutical Research*, **2(1)**, 51–61.

Case M. D. and Morgan T. M. (2003) Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology*, **3**, 7.

Lin D. Y., Shen L., Ying Z. and Breslow N. E. (1996) Group seqential designs for monitoring survival probabilities. *Biometrics*, **52**, 1033–1042.

Simon R. (1989) Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials*, **10**, 1–10.

See Also

OptimDes, SimDes

Examples

```
## Not run:
### single arm trial

B.init <- c(1, 2, 3, 4, 5)
m.init <- c(15, 20, 25, 20, 15)
alpha <- 0.05
beta <- 0.1
param <- c(1, 1.09, 2, 1.40)
x <- 1

# H0: S0=0.40 H1: S1=0.60
```

```
shape0 <- param[1]
scale0 <- param[2]
shape1 <- param[3]
scale1 <- param[4]

object1 <- OptimDes(B.init,m.init,alpha,beta,param,x,target="EDA",sf="futility",num.arm=1,num.stage=2)
n <- object1$n[2]
t1 <- object1$stageTime[1]
C1 <- object1$boundary[1]
C1U <- object1$boundary[2]
C2 <- object1$boundary[3]
b <- length(B.init)
l <- rank(c(cumsum(m.init),n),ties.method="min")[b+1]
mda <- ifelse(l>1,B.init[l-1]+(B.init[l]-B.init[l-1])*(n-sum(m.init[1:(l-1)]))/m.init[l],B.init[l]*(n/m.init[l]

### set up values to create a stepwise uniform distribution for accrual
B <- B.init[1:l]
B[l] <- mda
xv <- c(0,B)
M <- m.init[1:l]
M[l] <- ifelse(l>1,n-sum(m.init[1:(l-1)]),n)
yv <- c(0,M/(diff(xv)*n),0)

# density function of accrual
dens.Y <- stepfun(xv,yv,f=1,right=TRUE)
# pool of time points to be simulated from
t.Y <- seq(0,mda,by=0.01)

# simulate study times of length n
sample.Y <- sample(t.Y,n,replace=TRUE,prob=dens.Y(t.Y))

# simulate failure times of length n under the alternative hypothesis
sample.T <- rweibull(n,shape=shape1,scale=scale1)

Y1 <- sample.Y[sample.Y<=t1]
T1 <- sample.T[sample.Y<=t1]
Y2 <- sample.Y[sample.Y>t1]
T2 <- sample.T[sample.Y>t1]

# event rate under null hypothesis
p0<-pweibull(x,shape=shape0,scale=scale0)

# interim analysis
TestStage(x, C1, C1U, C2, tan=t1,num.arm=1,num.stage=2,Y11=Y1, T11=T1, p0=p0)

# final analysis if the study continues
TestStage(x, C1, C1U, C2, tan=t1,num.arm=1,num.stage=2,Y11=Y1, T11=T1, p0=p0)

# simulate failure times of length n under the null hypothesis
sample.T <- rweibull(n,shape=shape0,scale=scale0)

Y1 <- sample.Y[sample.Y<=t1]
```

```
T1 <- sample.T[sample.Y<=t1]
Y2 <- sample.Y[sample.Y>t1]
T2 <- sample.T[sample.Y>t1]

# interim analysis
TestStage(x, C1, C1U, C2, tan=t1,num.arm=1,num.stage=2,Y11=Y1, T11=T1, p0=p0)

# final analysis if the study continues
TestStage(x, C1, C1U, C2, tan=mda+x,num.arm=1,num.stage=2,Y11=Y1, T11=T1, p0=p0,Y21=Y2,T21=T2)


## End(Not run)
```

`weibPmatch` *Compute the shape or scale parameter for a Weibull distribution so it has a specified event-free rate at a specified time.*

Description

Determine the shape or scale parameter of a Weibull distribution so it has event-free rate P0 at time x. If the shape is specified, the scale parameter is computed, and if the scale is specified, the shape parameter is computed.

Usage

```
weibPmatch(x, p0, shape, scale)
```

Arguments

`x`	Pre-specified time for the event-free endpoint (e.g., 1 year).
`p0`	Event-free rate at time x.
`shape`	If specified, the necessary scale parameter is computed
`scale`	If specified, the necessary shape parameter is computed

Details

The time and event-free rate must be supplied. Either the shape or scale parameter must also be specified, but not both. The R parameterization of the Weibull distribution is used.

Value

A single numerical value is returned, either the shape or scale parameter, depending on which is specified by the user.

Author(s)

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References

Johnson, N. L., Kotz, S. and Balakrishnan, N. (1995) Continuous Univariate Distributions, volume 1, chapter 21. Wiley, New York.

See Also

weibull.plot,pweibull, OptimDes

Examples

```
param <- c(1, 1.09, 2, 1.40)
x<-1

p0<-pweibull(x,param[1],param[2],lower=FALSE)
p1<-pweibull(x,param[3],param[4],lower=FALSE)

weibull.plot(param,x)

### equivalent to simple call
paramNew<-c(param[1], weibPmatch(x,p0,param[1]), param[3], weibPmatch(x,p1,param[3]))
weibull.plot(paramNew, x)

### null curve with different shape
paramNew<-c(3.0, weibPmatch(x,p0,3.0), param[3], weibPmatch(x,p1,param[3]))
weibull.plot(paramNew, x)

### alternative curve with different scale
paramNew<-c(param[1], param[2], weibPmatch(x,p1,scale=2), 2)
weibull.plot(paramNew, x)
```

---

weibull.plot *Plot Weibull Survival Curves*

Description

Plot Weibull survival curves with differences at a target time highlighted. Designed for use with the param values input to function OptimDes.

Usage

```
weibull.plot(param, x, l.type = 1:3, l.col = c("blue", "red"), ...)
```

Arguments

param	Events should be defined as poor outcomes. Computations and reporting are based on the proportion without an event at a pre-specified time, x. For constructing an optimal design, complete event-free distributions at all times must be specified for the control condition (Null), and for the alternative "effective" treatment. Weibull distributions are currently implemented. param is a vector of length 4: (shape null, scale null, shape alternative, scale alternative). The R parameterization of the Weibull distribution is used.
x	Pre-specified time for the event-free endpoint (e.g., 1 year).
l.type	Line types for the plot. Default is 1-3.
l.col	Line colors for the plot. Default is "blue" for the null survival curve, "red" for the alternative survival curve.
...	Further graphical arguments, see plot.default.

Author(s)

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References

Johnson, N. L., Kotz, S. and Balakrishnan, N. (1995) Continuous Univariate Distributions, volume 1, chapter 21. Wiley, New York.

See Also

dweibull, OptimDes, weibPmatch

Examples

```
param <- c(1, 1.09, 2, 1.40)
x <- 1

weibull.plot(param,x)
```

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