Package 'OneArm2stage'

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Title Phase II Single-Arm Two-Stage Designs with Time-to-Event Outcomes

Version 1.2.1

Description Two-stage design for single-arm phase II trials with time-to-event endpoints (e.g., clinical trials on immunotherapies among cancer patients) can be calculated using this package. Two notable advantages of the package: 1) It provides flexible choices from three design methods (optimal, minmax, and admissible), and 2) the power of the design is more accurately calculated using the exact variance in the one-sample log-rank test. The package can be used for 1) planning the sample sizes and other design parameters, and 2) conducting the interim and final analyses for the Go/No-go decisions. More details about the design method can be found in: Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). <doi:10.1002/pst.1983>.

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Repository CRAN

RoxygenNote 7.2.1

Imports survival, utils, flexsurv, IPDfromKM

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VignetteBuilder knitr

Config/testthat/edition 3

License GPL (>= 3)

Depends R (>= 3.5.0)

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Contents

`FitDat` *Fit Historical Survival Data Assuming the Failure Time Follows a Weibull Distribution*

Description

The function fits parametric models for the time-to-event data with the underlying distribution of the failure time assumed to be Weibull.

Usage

```
FitDat(data)
```

Arguments

`data`	a historical survival data sample, has to contain two variables 'Time' and 'Cens': *Time*, the time under observation during trial for each patient. *Cens*, the status indicator of patients (event = 1, censored = 0).

Value

fit.Weibull the fitted model assuming a Weibull distribution.
AIC the AIC value from the fitted model.
parameter.estimates the estimated parameters from the fitted model.

References

Wang, M., Rule, S., Zinzani, P. L., Goy, A., Casasnovas, O., Smith, S. D.,..., Robak, T. (2018). Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. The Lancet, 391(10121), 659–667. https://doi.org/10.1016/s0140-6736(17)33108-2

Examples

```
library(IPDfromKM)
# a sample dataset that we already extracted from Wang et al, 2018.
df<- read.csv(system.file("extdata", "df.csv", package = "OneArm2stage"))

# risk time points
trisk <- c(0,2,4,6,8,10,12,14,16,18,20,22,24)

# number of patients at risk at each risk time point
```

```
nrisk.radio <- c(124,120,115,110,107,104,103,95,46,18,11,8,0)

# Preprocess the raw coordinates into an proper format for reconstruct IPD
pre_radio <- preprocess(dat=df, trisk=trisk,
                    nrisk=nrisk.radio,totalpts=NULL,maxy=100)

#Reconstruct IPD
est_radio <- getIPD(prep=pre_radio,armID=0,tot.events=NULL)

# shift the IPD data into the proper format for 'FitDat()'
ipd <- est_radio$IPD
dat3 <- as.data.frame(cbind(rep(0, nrow(ipd)),ipd$time, ipd$status))
colnames(dat3) <- c("Entry", "Time", "Cens")

# use FitDat function to fit the historical dat
modelSelect <- FitDat(dat3)
modelSelect$AIC
# Weibull
# 301.7776

# check the estimated parameters from the modeling results
modelSelect$parameter.estimates
# $Weibull
# shape     scale
# 0.1133671 3.9939753
```

LRT *Conduct the Interim or Final Analysis Using the One-Sample Log-Rank Test for Two-Stage TTE Trials*

Description

Performs the one-sample log-rank test (OSLR) for the time-to-event data from two-stage Phase II clinical trials assuming the failure time follows a Weibull distribution. This can be used for designs with either unrestricted or restricted follow-up .

Usage

```
LRT(shape, S0, x0, data)
```

Arguments

shape	shape parameter for the Weibull distribution.
S0	the survival probability at a fixed time point x0 under the null hypothesis.
x0	a fixed time point when the survival probability is S0 under null.

`data` the time-to-event data for either the interim or final analysis from a two-stage survival trial, contains 2 variables:
time the time period under observation before the time of interim analysis (for interim analysis) or during entire trial (for final analysis) for each patient.
status the status indicator of patients (event = 1, censored = 0).

Value

z the OSLR test statistic for the interim or final analysis, depending on data used.
O the observed number of events.
E the expected number of events.

References

Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). Two-stage phase II survival trial design. Pharmaceutical Statistics. 2020;19:214-229. https://doi.org/10.1002/pst.1983

Examples

```
dat<- read.csv(system.file("extdata", "kj1_final.csv", package = "OneArm2stage"))
LRT(shape=1, S0=0.62, x0=2, data=dat)
# O       E       Z
# 18.0000 16.3598 -0.4055
```

`phase2.TTE` *Two-Stage Designs with TTE Outcomes Using the One-Sample Log-Rank Test*

Description

phase2.TTE() provides the clinical trial design solutions for two-stage trials with time-to-event outcomes based on the one-sample log-rank (OSLR) test. It calculates the design parameters (e.g., t1, n1, n, c1, c) using optimal, minmax and admissible methods.

Usage

```
phase2.TTE(
  shape,
  S0,
  x0,
  hr,
  tf,
  rate,
  alpha,
  beta,
  prStop = 0,
  q_value = 0.5,
  dfc1 = 0.001,
```

```
  dfc2 = 0.001,
  dfc3 = 0.001,
  maxEn = 10000,
  range = 1,
  t1_p1 = 0.2,
  t1_p2 = 1.2,
  c1_p = 0.25,
  nbpt_p = 11,
  pascote_p = 1.26,
  restricted = 0
)
```

Arguments

shape	shape parameter for the baseline hazard function assuming that the failure time follows a Weibull distribution.
S0	survival probability at the fixed time point x0 under the null hypothesis (i.e, H0).
x0	a fixed time point where the survival probability is S0 under the null.
hr	hazard ratio, hr < 1. s1=s0^hr, where s1 is the survival probability under the alternative hypothesis (i.e., HA) and s0 is that under H0.
tf	the follow-up time (restricted or unrestricted), the time period from the entry of the last patient to the end of the trial.
rate	a constant accrual rate. Please consider use a reasonable rate value. If the rate is too small, the function might throw an error.
alpha	type I error.
beta	type II error.
prStop	the lower limit of the early stopping probability under H0, with default=0.
q_value	the relative importance between the maximum sample size (n) and the expected sample size under H0 (ES) when deriving the design based on the admissible method. The default is 0.5 and the range is (0, 1). The smaller q_value is, the more importance is given to ES. The greater it is, the more importance is given to n.
dfc1	the value defines the stopping criterion of the optimization process in the min-max method with smaller values lead to more iterations, default=0.001. Change is not recommended.
dfc2	the value defines the stopping criterion of the optimization process in the optimal method, smaller values lead to more iterations, default=0.001. Change is not recommended.
dfc3	the value defines the stopping criterion of the optimization process in the admissible method, smaller values lead to more iterations, default=0.001. Change is not recommended.
maxEn	the maximum of the expected sample size under null, default= 10000. Change is not recommended.

range	the value defines how far the parameters can deviate from the last iteration in the computation of the second-stage design parameters, default=1. Change is not recommended.
t1_p1	this value defines the lower limit of the possible range of t1 depending on the single-stage accrual time, default=0.2. Change is not recommended.
t1_p2	this value defines the upper limit of the possible range of t1 depending on the single-stage accrual time, default=0.2. Change is not recommended.
c1_p	this value defines the initial center in the possible range of c1, default=0.25. Change is not recommended.
nbpt_p	this value defines the initial number of points checked within possible ranges for n, t1 and c1, default=11. Change is not recommended.
pascote_p	this value defines how fast the possible ranges of the two-stage design parameters shrink on each iteration, default=1.26. Change is not recommended.
restricted	whether using restricted (1) or unrestricted (0) follow-up, default = 0.

Value

The function returns a list that includes **Single_stage**, **Two_stage_Optimal**, **Two_stage_minmax**, and **Two_stage_Admissible**, etc.

Single_stage contains the design parameters for the single-stage design:

- *nsignle* the required sample size for the single-stage design.
- *tasingle* the estimated accrual time for the single-stage design.
- *csingle* the critical value for the single-stage design.

Two_stage_Optimal contains the design parameters for the two-stage design based on the optimal method (i.e., minimizing ES):

- *n1* and *n* required sample sizes in the two-stage design by the interim and final stage, respectively.
- *c1* and *c* critical values in the two-stage design for interim and final analysis, respectively.
- *t1* the interim analysis time in the two-stage design.
- *MTSL* the maximum total study length (the sum of the accrual time and the follow-up time).
- *ES* the expected sample size under null in the two-stage design.
- *PS* the probability of early stopping under null in the two-stage design.

Two_stage_minmax contains the design parameters for the two- stage design based on the minmax method (i.e., minimizing the total sample size, n), including the same parameters as for the optimal method.

Two_stage_Admissible contains the design parameters for the two-stage design based on the admissible method (i.e., a "compromise" between the optimal and the minmax method), including the same parameters as for the optimal method, as well as:

- *Rho* The expected loss. Between the total sample size n derived from the minmax and the optimal method, the admissible method calculates a design for each possible value of n. The design with the lowest Rho value (i.e., first row in the output) is the recommended design based on the admissible method with the specified q-value.

Other outputs:

- *param* The input values to the arguments.
- *difn_opSg* The difference in n between the single-stage design and the optimal two-stage designs.
- *difn_opminmax* The difference in n between the optimal and the minmax two-stage designs.
- *minmax.err* 0 or 1. If minmax.err=1, optimization for the minmax method is incomplete.
- *optimal.err* 0 or 1. If optimal.err=1, optimization for the optimal method is incomplete.
- *admiss.err* 0 or 1. If admiss.err=1, optimization for a given n value in the admissible method is incomplete.
- *admiss.null1* 0 or 1. If admiss.null1=1, the admissible result is unavailable due to incomplete optimization with either the minmax or the optimal method.
- *admiss.null2* 0 or 1. If admiss.null2=1, the admissible result is unavailable as either the minmax or the optimal result is unavailable.
- *admiss.null3* 0 or 1. If admiss.null3=1, the admissible result is unavailable as n in the minmax result and n in the optimal result are equal.

References

Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). Two-stage phase II survival trial design. Pharmaceutical Statistics. 2020;19:214-229. https://doi.org/10.1002/pst.1983

Examples

```
# 1. An example when q_value=0.1, i.e, more importance is given to ES.
# phase2.TTE(shape=0.5, S0=0.6, x0=3, hr=0.5, tf=1, rate=5,
#   alpha=0.05, beta=0.15, q_value=0.1, prStop=0, restricted=0)
# $param
#   shape  S0  hr alpha beta rate x0 tf q_value prStop restricted
# 1   0.5 0.6 0.5  0.05 0.15    5  3  1     0.1      0          0
#
# $Single_stage
#   nsingle tasingle  csingle
# 1      45        9 1.644854
#
# $Two_stage_Optimal
#   n1     c1  n      c     t1 MTSL    ES     PS
# 1 29 0.1389 48 1.6159 5.7421 10.6 37.29 0.5552
#
# $Two_stage_minmax
#   n1     c1  n      c     t1 MTSL      ES     PS
# 1 34 0.1151 45 1.6391 6.7952   10 38.9831 0.5458
#
# $Two_stage_Admissible
#      n1      c1  n      c     t1 MTSL      ES     PS      Rho
# 123  29  0.0705 47 1.6232 5.7261 10.4 37.2993 0.5281 38.26937
# 285  28  0.0792 48 1.6171 5.5663 10.6 37.2790 0.5316 38.35110
# 1701 31  0.0733 46 1.6293 6.0191 10.2 37.5828 0.5292 38.42452
# 170  33 -0.0405 45 1.6391 6.4245 10.0 38.7692 0.4839 39.39228
#
# $difn_opSg
# [1] 3
#
# $difn_opminmax
# [1] 3
#
# $minmax.err
# [1] 0
#
# $optimal.err
# [1] 0
#
# $admiss.err
# [1] 0
#
# $admiss.null1
# [1] 0
#
# $admiss.null2
# [1] 0
#
# $admiss.null3
# [1] 0

# 2. An example when q_value=0.75, i.e., more importance is given to n.
```

```
# phase2.TTE(shape=0.5, S0=0.6, x0=3, hr=0.5, tf=1, rate=5,
# alpha=0.05, beta=0.15, q_value=0.75, prStop=0, restricted=0)
# $param
#   shape  S0  hr alpha beta rate x0 tf q_value prStop restricted
# 1   0.5 0.6 0.5  0.05 0.15    5  3  1    0.75      0          0
#
# $Single_stage
#   nsingle tasingle  csingle
# 1      45        9 1.644854
#
# $Two_stage_Optimal
#   n1     c1  n      c     t1 MTSL    ES     PS
# 1 29 0.1389 48 1.6159 5.7421 10.6 37.29 0.5552
#
# $Two_stage_minmax
#   n1     c1  n      c     t1 MTSL      ES     PS
# 1 34 0.1151 45 1.6391 6.7952   10 38.9831 0.5458
#
# $Two_stage_Admissible
#      n1      c1  n      c     t1 MTSL      ES     PS      Rho
# 170  33 -0.0405 45 1.6391 6.4245 10.0 38.7692 0.4839 43.44230
# 1701 31  0.0733 46 1.6293 6.0191 10.2 37.5828 0.5292 43.89570
# 123  29  0.0705 47 1.6232 5.7261 10.4 37.2993 0.5281 44.57483
# 285  28  0.0792 48 1.6171 5.5663 10.6 37.2790 0.5316 45.31975
#
# $difn_opSg
# [1] 3
#
# $difn_opminmax
# [1] 3
#
# $minmax.err
# [1] 0
#
# $optimal.err
# [1] 0
#
# $admiss.err
# [1] 0
#
# $admiss.null1
# [1] 0
#
# $admiss.null2
# [1] 0
#
# $admiss.null3
# [1] 0
```

`Sim` *Calculate Empirical Power by Simulation for Two-Stage Designs Using One-Sample Log-Rank Test*

Description

Sim() can be used to calculate the empirical power and type-I error by simulation given the design parameters obtained from the two-stage designs using phase2.TTE().

Usage

```
Sim(
  shape,
  S0,
  S1,
  x0,
  tf,
  rate,
  t1,
  c1,
  c,
  n1,
  n,
  N,
  restricted = 0,
  seed = 123
)
```

Arguments

`shape`	shape parameter of the baseline hazard function assuming Weibull distribution.
`S0`	survival probability at a fixed time point x0 under the null hypothesis.
`S1`	survival probability at a fixed time point x0 under the alternative hypothesis.
`x0`	a fixed time point where the survival probabilities are known for both null and alternative hypotheses.
`tf`	the follow-up time, the time period from the entry of the last patient to the end of the trial.
`rate`	a constant accrual rate.
`t1`	the interim analysis time as given by the two-stage design.
`c1`	the critical value for the interim analysis as given by the two-stage design.
`c`	the critical value for the final analysis as given by the two-stage design.
`n1`	the required sample size for the interim analysis as given by the two-stage design.
`n`	the required total sample size for the entire trial as given by the two-stage design.
`N`	number of trials in the simulation.

restricted	if restricted = 0 (default value), unrestricted follow-up is used. If restricted = 1 or any other values, restricted follow-up is used.
seed	seed for random number generation.

Value

a numeric value that is either the empirical power (when S1=S0^hr) or the type I-error (when S1=S0).

Examples

```
# calculate empirical power and type I error given design parameters
Sim(shape=1, S0=0.62, S1=0.62^(0.467), x0=2, tf=2, rate=5, t1=3.0593,
    c1=-0.302, c=1.6135, n1=16, n=26, N=10000, seed=5868)
# empirical power
# 0.813

Sim(shape=1, S0=0.62, S1=0.62, x0=2, tf=2, rate=5, t1=3.0593,
    c1=-0.302, c=1.6135, n1=16, n=26, N=10000, seed=5868)
# empirical type-I error
# 0.037
```

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