

Package ‘EventPredInCure’

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Title Event Prediction Including Cured Population

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Description Predicts enrollment and events assumed enrollment and treatment-specific time-to-event models, and calculates test statistics for time-to-event data with cured population based on the simulation. Methods for prediction event in the existence of cured population are as described in : Chen, Tai-Tsang(2016) <[doi:10.1186/s12874-016-0117-3](https://doi.org/10.1186/s12874-016-0117-3)>.

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Author Bo Wei [aut, cre] (ORCID: <<https://orcid.org/0000-0002-4430-2882>>),
Kaifeng Lu [aut] (ORCID: <<https://orcid.org/0000-0002-6160-7119>>),
Brent McHenry [aut]

Maintainer Bo Wei <bowei1990@gmail.com>

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EventPredInCure-package

Event Prediction Including Cured Population

Description

Predicts enrollment and events using assumed enrollment and/or treatment-specific time-to-event models in the existence of the cured population. Calculate test statistics based on the simulated data sets from the assumed enrollment and/or treatment-specific time-to-event models in the existence of the cured population.

Details

Accurately predicting the date at which a target number of subjects or events will be achieved is critical for the planning, monitoring, and execution of clinical trials in the existence of the cured population. The EventPredInCure package provides enrollment and event prediction capabilities using assumed enrollment and treatment-specific time-to-event models and calculate test statistics based on the simulated data sets from the assumed enrollment and/or treatment-specific time-to-event models in the existence of the cured population.

At the design stage, enrollment is often specified using a piecewise Poisson process with a constant enrollment rate during each specified time interval. At the analysis stage, before enrollment completion, the EventPredInCure package considers several models, including the homogeneous Poisson model, the time-decay model with an enrollment rate function $\lambda(t) = \mu/\delta \times (1 - \exp(-\delta t))$, the B-spline model with the daily enrollment rate $\lambda(t) = \exp(B(t) \times \theta)$, and the piecewise Poisson model. If prior information exists on the model parameters, it can be combined with the likelihood to yield the posterior distribution.

The EventPredInCure package offers several time-to-event models without cured-population, including exponential, Weibull, log-logistic, log-normal, piecewise exponential, model averaging of Weibull and log-normal, and spline. The models including exponential, Weibull, log-logistic, log-normal, piecewise exponential are extended to account cured-population. In the design stage, the models including exponential, Weibull, log-logistic, log-normal, piecewise exponential are also extended for delayed treatment effect setting (only for generating simulated data sets in the design stage). For time to dropout, the same set of model without cured-population and delayed treatment effect options are considered. If enrollment is complete, ongoing subjects who have not had the event of interest or dropped out of the study before the data cut contribute additional events in the future. Their event times are generated from the conditional distribution given that they have survived at the data cut. For new subjects that need to be enrolled, their enrollment time and event time can be generated from the specified enrollment and time-to-event models with parameters drawn from the posterior distribution. Time-to-dropout can be generated in a similar fashion.

The EventPredInCure package displays the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC) and a fitted curve overlaid with observed data to help users select the most appropriate model for enrollment and event prediction. Prediction intervals in the prediction plot can be used to measure prediction uncertainty, and the simulated enrollment and event data can be used for further data exploration.

The most useful function in the EventPredInCure package is `getPrediction`, which combines model fitting, data simulation, and a summary of simulation results. Other functions perform individual tasks and can be used to select an appropriate prediction model.

The EventPredInCure package implements a model parameterization that enhances the asymptotic normality of parameter estimates. Specifically, the package utilizes the following parameterization to achieve this goal:

- Enrollment models
 - Poisson: $\theta = \log(\text{rate})$
 - Time-decay: $\theta = c(\log(\mu), \log(\delta))$
 - B-spline: no reparametrization is needed. The knots as considered fixed.
 - Piecewise Poisson: $\theta = \log(\text{rates})$. The left endpoints of time intervals, denoted as `accrualTime`, are considered fixed.
- Event or dropout models

- Exponential: $\theta = \log(\text{rate})$
- Weibull: $\theta = c(\log(\text{scale}), -\log(\text{shape}))$
- Log-logistic: $\theta = c(\log(\text{scale}), -\log(\text{shape}))$
- Log-normal: $\theta = c(\text{meanlog}, \log(\text{sdlog}))$
- Piecewise exponential: $\theta = \log(\text{rates})$. The left endpoints of time intervals, denoted as `piecewiseSurvivalTime` for event model and `piecewiseDropoutTime` for dropout model, are considered fixed.
- Model averaging: $\theta = c(\log(\text{weibull}\$\text{scale}), -\log(\text{weibull}\$\text{shape}), \text{lnorm}\$\text{meanlog}, \log(\text{lnorm}\$\text{sdlog}))$. The covariance matrix for θ is structured as a block diagonal matrix, with the upper-left block corresponding to the Weibull component and the lower-right block corresponding to the log-normal component. In other words, the covariance matrix is partitioned into two distinct blocks, with no off-diagonal elements connecting the two components. The weight assigned to the Weibull component, denoted as `w1`, is considered fixed.
- Spline: θ corresponds to the coefficients of basis vectors. The knots and scale are considered fixed. The scale can be hazard, odds, or normal, corresponding to extensions of Weibull, log-logistic, and log-normal distributions, respectively.

The `EventPredInCure` package uses days as its primary time unit. If you need to convert enrollment or event rates per month to rates per day, simply divide by 30.4375.

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.
- Royston, Patrick, and Mahesh KB Parmar. "Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects." *Statistics in medicine* 21.15 (2002): 2175-2197.
- Bagiella, Emilia, and Daniel F. Heitjan. "Predicting analysis times in randomized clinical trials." *Statistics in medicine* 20.14 (2001): 2055-2063.
- Ying, Gui-shuang, and Daniel F. Heitjan. "Weibull prediction of event times in clinical trials." *Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry* 7.2 (2008): 107-120.
- Zhang, Xiaoxi, and Qi Long. "Stochastic modeling and prediction for accrual in clinical trials." *Statistics in Medicine* 29.6 (2010): 649-658.

b4pst

Function to calculate survival time and censor variables before and post a time lag (delay treatment effect time)

Description

calculate survival time and censor variables before and post a time lag.

Usage

```
b4pst(os, osc, lag)
```

Arguments

| | |
|-----|---------------------------------------|
| os | a vector to denote the observed times |
| osc | a vector to denote censor variables |
| lag | a scalar to denote the time lag |

Value

A list including the following variables:

- b4os: overall survival time before the time lag
- b4osc: censor variable before the time lag
- pstos: overall survival time post the time lag
- pstosc: censor variable post the time log lag

Examples

```
n <- 500
event <- runif(n,1, 5)
osc<-1*(event<=4)
os <- pmin(event,4)
b4pst(os,osc,3.5)
```

Chen_2016_event_time *Function to generate event time in the existence of cured population*

Description

generate event time under the delay-treatment effect and cured population setting

Usage

```
Chen_2016_event_time(u, hr, distribution, p, lag, a, b, mu, sd)
```

Arguments

| | |
|--------------|--|
| u | a scalar with between 0 and 1 |
| hr | hazard ratio if this subject in the corresponding arm vs control arm |
| distribution | the distribution for the control arm, valid values of inputs include: exponential, weibull, log-normal, log-logistic |
| p | the proportion of cured population in the control arm |

| | |
|-----|---|
| lag | delayed treatment effect time after treatment initialization, when the hr between treatment arm and control =1 until lag time |
| a | the shape parameter in the Weibull or the log-logistic distribution |
| b | the scale parameter in the exponential, Weibull or the log-logistic distribution |
| mu | the mean in the log-normal distribution |
| sd | the standard deviation in the log-normal distribution |

Value

the event time

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." BMC medical research methodology 16.1 (2016): 1-10.

Chen_2016_event_time_abovetime0

Function to generate event time based on Chen 2016 method for ongoing subject

Description

generate event time under the delay-treatment effect and cured population setting given $T > \text{time0}$

Usage

Chen_2016_event_time_abovetime0(u, distribution, p, time0, a, b, mu, sd)

Arguments

| | |
|--------------|--|
| u | a scalar with between 0 and 1 |
| distribution | the distribution for the control arm, valid values of inputs include: exponential, weibull, log-normal, log-logistic |
| p | the proportion of cured population in the control arm |
| time0 | the observed ongoing survival time |
| a | the shape parameter in the Weibull or the log-logistic distribution |
| b | the scale parameter in the exponential, Weibull or the log-logistic distribution |
| mu | the mean in the log-normal distribution |
| sd | the standard deviation in the log-normal distribution |

Value

the event time

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

Chen_2016_event_time_piecewise_exp_abovetime0

Function to generate event time with piecewise exponential distribution for ongoing subject in the existence of cured population

Description

generate event time under the delay-treatment effect and cured population setting

Usage

```
Chen_2016_event_time_piecewise_exp_abovetime0(
  u,
  p,
  time0 = 0,
  piecewiseSurvivalTime = 0,
  piecewisehazard
)
```

Arguments

| | |
|-----------------------|---|
| u | a scalar with between 0 and 1, which is the conditional survival probability at the event time. |
| p | the proportion of cured population in the control arm |
| time0 | the observed ongoing survival time |
| piecewiseSurvivalTime | A vector that specifies the time intervals for the piecewise exponential survival distribution. Must start with 0, e.g., c(0, 60) breaks the time axis into 2 event intervals: [0, 60) and [60, Inf). By default, it is set to 0. |
| piecewisehazard | A vector that specifies the hazard rate in intervals for the piecewise exponential survival distribution. |

Value

the event time

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

FH_test

*Fleming-Harrington weighted log-rank tests***Description**

Calculating the Fleming-Harrington weighted log-rank tests

Usage

```
FH_test(survival, delta, trt, rho, gamma, test = c("Futility"))
```

Arguments

| | |
|----------|--|
| survival | Time to event or censoring. |
| delta | Event indicators. |
| trt | Treatment assignment indicator with 1 denoting the treated group, and 0 denoting the placebo group. |
| rho | First power parameter for the Fleming-Harrington weight which weighs on the early departures: $S(t^-)^\rho(1 - S(t^-))^\gamma$. |
| gamma | Second power parameter for the Fleming-Harrington weight which weighs on the late departures: $S(t^-)^\rho(1 - S(t^-))^\gamma$. |
| test | a character denotes the test type, include "Superiority", "Futility", "Two-sided" |

Value

A list 3 different components

| | |
|--------|---|
| O1 | Observed number of weighted events (with a multiplication of corresponding weights) in the treatment arm. |
| E1 | Expected number of weighted events (with a multiplication of corresponding weights) in the treatment arm. |
| Z | Weighted log-rank test statistic. |
| pvalue | Weighted log-rank test statistic pvalue |

Examples

```
n <- 500
event <- runif(n,1, 5)
osc<-1*(event<=4)
os <- pmin(event,4)
trt<-c(rep(0,n/2),rep(1,n/2))
FH_test(os,osc,trt,rho=1,gamma=0)
```

| | |
|-----------|--|
| finalData | <i>Final enrollment and event data after achieving the target number of events</i> |
|-----------|--|

Description

A data frame with 300 rows and 7 columns:

trialsdt The trial start date
usubjid The unique subject ID
randdt The randomization date
treatment The treatment group number
treatment_description Description of the treatment group
time The day of event or censoring since randomization
event The event indicator: 1 for event, 0 for non-event
dropout The dropout indicator: 1 for dropout, 0 for non-dropout
cutoffdt The cutoff date

For ongoing subjects, both event and dropout are equal to 0.

Usage

```
finalData
```

Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 300 rows and 9 columns.

| | |
|------------|----------------------------------|
| fitDropout | <i>Fit time-to-dropout model</i> |
|------------|----------------------------------|

Description

Fits a specified time-to-dropout model to the dropout data.

Usage

```
fitDropout(  
  df,  
  dropout_model = "exponential",  
  piecewiseDropoutTime = 0,  
  by_treatment = FALSE,  
  criterion = "both"  
)
```

| | |
|---------------|-----------------------------|
| fitEnrollment | <i>Fit enrollment model</i> |
|---------------|-----------------------------|

Description

Fits a specified enrollment model to the enrollment data.

Usage

```
fitEnrollment(
  df,
  enroll_model = "b-spline",
  nknots = 0,
  accrualTime = 0,
  criterion = "both"
)
```

Arguments

| | |
|--------------|---|
| df | The subject-level enrollment data, including trialsdt, randdt and cutoffdt. |
| enroll_model | The enrollment model which can be specified as "Poisson", "Time-decay", "B-spline", or "Piecewise Poisson". By default, it is set to "B-spline". |
| nknots | The number of inner knots for the B-spline enrollment model. By default, it is set to 0. |
| accrualTime | The accrual time intervals for the piecewise Poisson model. Must start with 0, e.g., c(0, 30) breaks the time axis into 2 accrual intervals: [0, 30) and [30, Inf). By default, it is set to 0. |
| criterion | A character variable to denote the criterion in model selection to shown in the figure, which can be set to one of the following options: "aic","bic" or "both". By default,it is set to both. |

Details

For the time-decay model, the mean function is $\mu(t) = \mu/\delta * (t - 1/\delta * (1 - \exp(-\delta * t)))$ and the rate function is $\lambda(t) = \mu/\delta * (1 - \exp(-\delta * t))$. For the B-spline model, the daily enrollment rate is approximated as $\lambda(t) = \exp(B(t) * \theta)$, where $B(t)$ represents the B-spline basis functions.

Value

A list of results from the model fit including key information such as the enrollment model, model, the estimated model parameters, theta, the covariance matrix, vtheta, and the Bayesian Information Criterion, bic, and Akaike Information Criterion, aic, as well as the design matrix x for the B-spline enrollment model, and accrualTime for the piecewise Poisson enrollment model.

The fitted enrollment curve is also returned.

References

- Zhang, Xiaoxi, and Qi Long. "Stochastic modeling and prediction for accrual in clinical trials." *Statistics in Medicine* 29.6 (2010): 649-658.

Examples

```
enroll_fit <- fitEnrollment(df = interimData1, enroll_model = "b-spline",
                           nknots = 1)
```

| | |
|----------|--------------------------------|
| fitEvent | <i>Fit time-to-event model</i> |
|----------|--------------------------------|

Description

Fits a specified time-to-event model to the event data.

Usage

```
fitEvent(
  df,
  event_model = "model averaging",
  piecewiseSurvivalTime = 0,
  k = 0,
  scale = "hazard",
  by_treatment = FALSE,
  criterion = "both"
)
```

Arguments

| | |
|-------------|---|
| df | The subject-level event data, including time and event. The data should also include treatment coded as 1, 2, and so on, and treatment_description for fitting the event model by treatment. |
| event_model | The event model used to analyze the event data which can be set to one of the following options: "exponential", "Weibull", "log-logistic", "log-normal", "piecewise exponential", "model averaging", "spline", "exponential with cured population", "weibull with cured population", "log-normal with cured population", "log-logistic with cured population" or "piecewise exponential with cured population". The model averaging uses the $\exp(-bic/2)$ weighting and combines Weibull and log-normal models. The spline model of Royston and Parmar (2002) assumes that a transformation of the survival function is modeled as a natural cubic spline function of log time. By default, it is set to "model averaging". |

| | |
|---------------|--|
| getPrediction | <i>Enrollment and event prediction</i> |
|---------------|--|

Description

Performs enrollment and event prediction by utilizing observed data and specified enrollment and event models.

Usage

```
getPrediction(  
  df = NULL,  
  to_predict = "enrollment and event",  
  target_n = NA,  
  target_d = NA,  
  enroll_model = "b-spline",  
  nknots = 0,  
  lags = 30,  
  accrualTime = 0,  
  enroll_prior = NULL,  
  event_model = "exponential",  
  piecewiseSurvivalTime = 0,  
  k = 0,  
  scale = "hazard",  
  event_prior = NULL,  
  dropout_model = "exponential",  
  piecewiseDropoutTime = 0,  
  dropout_prior = NULL,  
  fixedFollowup = FALSE,  
  followupTime = 365,  
  pilevel = 0.9,  
  nyears = 4,  
  nreps = 500,  
  showEnrollment = TRUE,  
  showEvent = TRUE,  
  showDropout = FALSE,  
  showOngoing = FALSE,  
  by_treatment = FALSE,  
  ngroups = 1,  
  alloc = NULL,  
  treatment_label = NULL,  
  criterion = "both",  
  seed.num = NULL  
)
```

Arguments

| | |
|-----------------------|---|
| df | The subject-level enrollment and event data, including trialsdt, usubjid, randdt, and cutoffdt for enrollment prediction, and, additionally, time, event, and dropout for event prediction. The data should also include treatment coded as 1, 2, and so on, and treatment_description for enrollment and event prediction by treatment. By default, it is set to NULL for enrollment and event prediction at the design stage. |
| to_predict | Specifies what to predict: "enrollment only", "event only", or "enrollment and event". By default, it is set to "enrollment and event". |
| target_n | The target number of subjects to enroll in the study. |
| target_d | The target number of events to reach in the study. |
| enroll_model | The enrollment model which can be specified as "Poisson", "Time-decay", "B-spline", "Piecewise Poisson" or "Piecewise Uniform". By default, it is set to "B-spline". |
| nknots | The number of inner knots for the B-spline enrollment model. By default, it is set to 0. |
| lags | The day lags to compute the average enrollment rate to carry forward for the B-spline enrollment model. By default, it is set to 30. |
| accrualTime | The accrual time intervals for the piecewise Poisson model. Must start with 0, e.g., c(0, 30) breaks the time axis into 2 accrual intervals: [0, 30) and [30, Inf). By default, it is set to 0. |
| enroll_prior | The prior of enrollment model parameters. |
| event_model | The event model used to analyze the event data which can be set to one of the following options: "exponential", "Weibull", "log-logistic", "log-normal", "piecewise exponential", "model averaging", "exponential with cured population", "weibull with cured population", "log-normal with cured population", "log-logistic with cured population", or "piecewise exponential with cured population". For the design stage analysis, there are additional options: "exponential with cured population and delayed treatment", "weibull with cured population and delayed treatment", "log-normal with cured population and delayed treatment", "log-logistic with cured population and delayed treatment". The model averaging uses the $\exp(-bic/2)$ weighting and combines Weibull and log-normal models. By default, it is set to "exponential". |
| piecewiseSurvivalTime | A vector that specifies the time intervals for the piecewise exponential survival distribution, or piecewise exponential with cured population. Must start with 0, e.g., c(0, 60) breaks the time axis into 2 event intervals: [0, 60) and [60, Inf). By default, it is set to 0. |
| k | The number of inner knots of the spline event model of Royston and Parmar (2002). The default $k=0$ gives a Weibull, log-logistic or log-normal model, if scale is "hazard", "odds", or "normal", respectively. The knots are chosen as equally-spaced quantiles of the log uncensored survival times. The boundary knots are chosen as the minimum and maximum log uncensored survival times. |
| scale | If "hazard", the log cumulative hazard is modeled as a spline function. If "odds", the log cumulative odds is modeled as a spline function. If "normal", $-\text{qnorm}(S(t))$ is modeled as a spline function. |

| | |
|----------------------|--|
| event_prior | The prior of event model parameters. |
| dropout_model | The dropout model used to analyze the dropout data which can be set to one of the following options: "exponential", "Weibull", "log-logistic", "log-normal", or "piecewise exponential". By default, it is set to "exponential". |
| piecewiseDropoutTime | A vector that specifies the time intervals for the piecewise exponential dropout distribution. Must start with 0, e.g., c(0, 60) breaks the time axis into 2 event intervals: [0, 60) and [60, Inf). By default, it is set to 0. |
| dropout_prior | The prior of dropout model parameters. |
| fixedFollowup | A Boolean variable indicating whether a fixed follow-up design is used. By default, it is set to FALSE for a variable follow-up design. |
| followupTime | The follow-up time for a fixed follow-up design, in days. By default, it is set to 365. |
| pilevel | The prediction interval level. By default, it is set to 0.90. |
| nyears | The number of years after the data cut for prediction. By default, it is set to 4. |
| nreps | The number of replications for simulation. By default, it is set to 500. |
| showEnrollment | A Boolean variable to control whether or not to show the number of enrolled subjects. By default, it is set to TRUE. |
| showEvent | A Boolean variable to control whether or not to show the number of events. By default, it is set to TRUE. |
| showDropout | A Boolean variable to control whether or not to show the number of dropouts. By default, it is set to FALSE. |
| showOngoing | A Boolean variable to control whether or not to show the number of ongoing subjects. By default, it is set to FALSE. |
| by_treatment | A Boolean variable to control whether or not to predict by treatment group. By default, it is set to FALSE. |
| ngroups | The number of treatment groups for enrollment prediction at the design stage. By default, it is set to 1. It is replaced with the actual number of treatment groups in the observed data if df is not NULL. |
| alloc | The treatment allocation in a randomization block. By default, it is set to NULL, which yields equal allocation among the treatment groups. |
| treatment_label | The treatment labels for treatments in a randomization block for design stage prediction. |
| criterion | A character variable to denote the criterion in model selection to shown in the figure, which can be set to one of the following options: "aic", "bic" or "both". By default, it is set to both. |
| seed.num | The number of the random seed. The default is NULL. |

Details

For the time-decay model, the mean function is $\mu(t) = \mu/\delta*(t - 1/\delta*(1 - \exp(-\delta*t)))$ and the rate function is $\lambda(t) = \mu/\delta*(1 - \exp(-\delta*t))$. For the B-spline model, the

daily enrollment rate is approximated as $\lambda(t) = \exp(B(t) * \theta)$, where $B(t)$ represents the B-spline basis functions.

The `enroll_prior` variable should be a list that includes `model` to specify the enrollment model (poisson, time-decay, piecewise poisson, or piecewise uniform), `theta` and `vtheta` to indicate the parameter values and the covariance matrix. One can use a very small value of `vtheta` to fix the parameter values. For the piecewise Poisson enrollment or piecewise uniform rate model, the list should also include `accrualTime`. It should be noted that the B-spline model is not appropriate for use as prior.

For event prediction by treatment with prior information, the `event_prior` variable should be a list with one element per treatment. For each treatment, the element should include `model` to specify the event (dropout) model (exponential, weibull, log-logistic, log-normal, or piecewise exponential, weibull with cured population, exponential with cured population, log-normal with cured population, log-logistic with cured population, piecewise exponential with cured population, exponential with cured population and delayed treatment, weibull with cured population and delayed treatment, log-normal with cured population and delayed treatment, log-logistic with cured population and delayed treatment), `theta` and `vtheta` to indicate the parameter values and the covariance matrix. For the piecewise exponential or piecewise exponential with cured population or piecewise exponential with cured population and delayed treatment event model, the list should also include `piecewiseSurvivalTime` to indicate the location of knots. It should be noted that the model averaging and spline options are not appropriate for use as prior.

The `dropout_prior` should be a list with one element per treatment. For each treatment, the element should include `w` to specify the weight of the treatment in a randomization block, `model` to specify the dropout model (exponential, weibull, log-logistic, log-normal, or piecewise exponential), `theta` and `vtheta` to indicate the parameter values and the covariance matrix. For the piecewise exponential dropout model, the list should also include `piecewiseDropoutTime` to indicate the location of knots.

If the event prediction is not by treatment while the prior information is given by treatment, then each element of `event_prior` (`dropout_prior`) should also include `w` to specify the weight of the treatment in a randomization block. This method can only be used in the event prior with exponential, weibull, log-logistic, log-normal, or piecewise exponential.

If the prediction is not by treatment and the prior is given for the overall study, then `event_prior` (`dropout_prior`) is a flat list with `model`, `theta`, and `vtheta`. For the piecewise exponential event (dropout) model, it should also include `piecewiseSurvivalTime` (`piecewiseDropoutTime`) to indicate the location of knots.

For analysis-stage enrollment and event prediction, the `enroll_prior`, `event_prior`, and `dropout_prior` are either set to NULL to use the observed data only, or specify the prior distribution of model parameters to be combined with observed data likelihood for enhanced modeling flexibility.

Value

A list that includes the fits of observed data models, as well as simulated enrollment data for new subjects and simulated event data for ongoing and new subjects.

Examples

```
fit1 <- list(model = "piecewise uniform",
            theta = -0.58,
```

```

vtheta=0, accrualTime =0)

fit2<-list()
fit2[[1]] <- list(model = "weibull with cured population and delayed treatment",
                 theta = c(-2.2,0,6.5,0,1),
                 vtheta = matrix(0,5,5))
fit2[[2]] <- list(model = "weibull with cured population and delayed treatment",
                 theta = c(-2.2,0,6.5,46,0.65),
                 vtheta = matrix(0,5,5))

fit3 <- list()

fit3[[1]] <- list(model = "exponential",
                 theta =log(0.0003),
                 vtheta=0)
fit3[[2]] <- list(model = "exponential",
                 theta =log(0.0003),
                 vtheta=0)

getPrediction(target_n=200,target_d=60,lags=46,enroll_prior=fit1,
             event_prior=fit2,
             dropout_prior=fit3,ngroups=2)

```

interimData1

Interim enrollment and event data before enrollment completion

Description

A data frame with 225 rows and 9 columns:

trialsdt The trial start date
usubjid The unique subject ID
randdt The randomization date
treatment The treatment group number
treatment_description Description of the treatment group
time The day of event or censoring since randomization
event The event indicator: 1 for event, 0 for non-event
dropout The dropout indicator: 1 for dropout, 0 for non-dropout
cutoffdt The cutoff date

For ongoing subjects, both event and dropout are equal to 0.

Usage

```
interimData1
```

Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 224 rows and 9 columns.

| | |
|--------------|--|
| interimData2 | <i>Interim enrollment and event data after enrollment completion</i> |
|--------------|--|

Description

A data frame with 300 rows and 7 columns:

`trialsdt` The trial start date

`usubjid` The unique subject ID

`randdt` The randomization date

`treatment` The treatment group number

`treatment_description` Description of the treatment group

`time` The day of event or censoring since randomization

`event` The event indicator: 1 for event, 0 for non-event

`dropout` The dropout indicator: 1 for dropout, 0 for non-dropout

`cutoffdt` The cutoff date

For ongoing subjects, both event and dropout are equal to 0.

Usage

```
interimData2
```

Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 300 rows and 9 columns.

| | |
|--------------------------------------|---|
| <code>loglik_Chen_exponential</code> | <i>Log-likelihood function for exponential distribution with cured population</i> |
|--------------------------------------|---|

Description

Provide log-likelihood function for exponential distribution with cured population

Usage

```
loglik_Chen_exponential(par, df)
```

Arguments

- `par` a vector with two elements, where the first element denotes the logistic of the proportion of the cured population, and the second element denotes the log of the hazard rate.
- `df` The subject-level event data, including `time` and `event`.

Value

The negative value of the log-likelihood function given parameter `par` and the dataset `df`

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

`loglik_Chen_log_logistic`

Log-likelihood function for log-logistic distribution with cured population

Description

Provide log-likelihood function for log-logistic distribution with cured population

Usage

```
loglik_Chen_log_logistic(par, df)
```

Arguments

- `par` a vector with three elements, where the first element denotes the logistic of the proportion of the cured population, and the second element and the third element denote the log of shape and the log of the scale parameter of the log-logistic distribution.
- `df` The subject-level event data, including `time` and `event`.

Value

The negative value of the log-likelihood function given parameter `par` and the dataset `df`

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

`loglik_Chen_log_normal`*Log-likelihood function for log-normal distribution with cured population*

Description

Provide log-likelihood function for log-normal distribution with cured population

Usage

```
loglik_Chen_log_normal(par, df)
```

Arguments

| | |
|------------------|--|
| <code>par</code> | a vector with three elements, where the first element denotes the logistic of the proportion of the cured population, and the second element and the third element denote the mean and the log of standard deviation parameter of the log-normal distribution. |
| <code>df</code> | The subject-level event data, including time and event. |

Value

The negative value of the log-likelihood function given parameter `par` and the dataset `df`

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

`loglik_Chen_piecewise_exponential`*Log-likelihood function for piecewise-exponential distribution with cured population*

Description

Provide log-likelihood function for piecewise-exponential distribution with cured population

Usage

```
loglik_Chen_piecewise_exponential(par = NULL, df, piecewiseSurvivalTime)
```

Arguments

- `par` a vector with $m+1$ elements, where the first element denotes the logistic of the proportion of the cured population, and the rest element denotes the log of the hazard rate in intervals
- `df` The subject-level event data, including `time` and `event`.
- `piecewiseSurvivalTime`
A vector with length m that specifies the time intervals for the piecewise exponential survival distribution. Must start with 0, e.g., `c(0, 60)` breaks the time axis into 2 event intervals: `[0, 60)` and `[60, Inf)`. By default, it is set to 0.

Value

The negative value of the log-likelihood function given parameter `par` and the dataset `df`

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

`loglik_Chen_weibull` *Log-likelihood function for Weibull distribution with cured population*

Description

Provide log-likelihood function for Weibull distribution with cured population

Usage

```
loglik_Chen_weibull(par, df)
```

Arguments

- `par` a vector with three elements, where the first element denotes the logistic of the proportion of the cured population, and the second element and the third element denote the log of the shape and log of the scale parameter of the Weibull distribution.
- `df` The subject-level event data, including `time` and `event`.

Value

The negative value of the log-likelihood function given parameter `par` and the dataset `df`

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

predictEnrollment *Predict enrollment*

Description

Utilizes a pre-fitted enrollment model to generate enrollment times for new subjects and provide a prediction interval for the expected time to reach the enrollment target.

Usage

```
predictEnrollment(
  df = NULL,
  target_n,
  enroll_fit,
  lags = 1,
  pilevel = 0.9,
  nyears = 4,
  nreps = 500,
  by_treatment = FALSE,
  ngroups = 1,
  alloc = NULL,
  treatment_label = NULL,
  seed.num = NULL
)
```

Arguments

| | |
|--------------|--|
| df | The subject-level enrollment data, including <code>trialsdt</code> , <code>randdt</code> and <code>cutoffdt</code> . The data should also include <code>treatment</code> coded as 1, 2, and so on, and <code>treatment_description</code> for prediction by treatment group. By default, it is set to <code>NULL</code> for enrollment prediction at the design stage. |
| target_n | The target number of subjects to enroll in the study. |
| enroll_fit | The pre-fitted enrollment model used to generate predictions. |
| lags | The day lags to compute the average enrollment rate to carry forward for the B-spline enrollment model. By default, it is set to 1. |
| pilevel | The prediction interval level. By default, it is set to 0.90. |
| nyears | The number of years after the data cut for prediction. By default, it is set to 4. |
| nreps | The number of replications for simulation. By default, it is set to 500. |
| by_treatment | A Boolean variable to control whether or not to predict enrollment by treatment group. By default, it is set to <code>FALSE</code> . |
| ngroups | The number of treatment groups for enrollment prediction at the design stage. By default, it is set to 1. It is replaced with the actual number of treatment groups in the observed data if <code>df</code> is not <code>NULL</code> . |
| alloc | The treatment allocation in a randomization block. By default, it is set to <code>NULL</code> , which yields equal allocation among the treatment groups. |

| | |
|-----------------|---|
| treatment_label | The treatment labels for treatments in a randomization block for design stage prediction. |
| seed.num | The number of the random seed. The default is NULL. |

Details

The `enroll_fit` variable can be used for enrollment prediction at the design stage. A piecewise uniform can be parameterized through the time intervals, `accrualTime`, which is treated as fixed, and the enrollment rates in the intervals, `accrualrate`, the number of patients in each intervals. A piecewise Poisson model can be parameterized through the time intervals, `accrualTime`, which is treated as fixed, and the enrollment rates in the intervals, `accrualIntensity`, the log of which is used as the model parameter. For the homogeneous Poisson, time-decay, and piecewise Poisson models, `enroll_fit` is used to specify the prior distribution of model parameters, with a very small variance being used to fix the parameter values. It should be noted that the B-spline model is not appropriate for use during the design stage.

During the enrollment stage, `enroll_fit` is the enrollment model fit based on the observed data. The fitted enrollment model is used to generate enrollment times for new subjects.

Value

A list of prediction results, which includes important information such as the median, lower and upper percentiles for the estimated time to reach the target number of subjects, as well as simulated enrollment data for new subjects. The data for the prediction plot is also included within the list.

References

Xiaoxi Zhang and Qi Long. Stochastic modeling and prediction for accrual in clinical trials. *Stat in Med.* 2010; 29:649-658.

Examples

```
# Enrollment prediction at the design stage
fit1 <- list(model = "piecewise uniform",
            theta = -0.58,
            vtheta=0, accrualTime =0)

predictEnrollment(df = NULL, target_n=200, enroll_fit = fit1,lags=46,
                 pilevel=0.9, nyears=4, nreps=100,by_treatment=TRUE,
                 ngroups=2, alloc=c(1,1), treatment_label=c('a','b'))
```

predictEvent

Predict event time for ongoing subjects with or without cured population.

Description

Utilizes pre-fitted time-to-event and time-to-dropout models to generate event and dropout times for ongoing subjects and new subjects. It also provides a prediction interval for the expected time to reach the target number of events.

Usage

```
predictEvent(
  df = NULL,
  target_d,
  newSubjects = NULL,
  event_fit,
  dropout_fit = NULL,
  fixedFollowup = FALSE,
  followupTime = 365,
  pilevel = 0.9,
  nyears = 4,
  nreps = 500,
  showEnrollment = TRUE,
  showEvent = TRUE,
  showDropout = FALSE,
  showOngoing = FALSE,
  by_treatment = FALSE,
  seed.num = NULL
)
```

Arguments

| | |
|---------------|--|
| df | The subject-level enrollment and event data, including randdt, cutoffdt, time, event, and dropout. By default, it is set to NULL for event prediction at the design stage. |
| target_d | The target number of events to reach in the study. |
| newSubjects | The enrollment data for new subjects including draw and arrivalTime. By default, it is set to NULL, indicating the completion of subject enrollment. |
| event_fit | The pre-fitted event model used to generate predictions. |
| dropout_fit | The pre-fitted dropout model used to generate predictions. By default, it is set to NULL, indicating no dropout. |
| fixedFollowup | A Boolean variable indicating whether a fixed follow-up design is used. By default, it is set to FALSE for a variable follow-up design. |
| followupTime | The follow-up time for a fixed follow-up design, in days. By default, it is set to 365. |
| pilevel | The prediction interval level. By default, it is set to 0.90. |
| nyears | The number of years after the data cut for prediction. By default, it is set to 4. |
| nreps | The number of replications for simulation. By default, it is set to 500. If newSubjects is not NULL, the number of draws in newSubjects should be nreps. |

| | |
|----------------|--|
| showEnrollment | A Boolean variable to control whether or not to show the number of enrolled subjects. By default, it is set to TRUE. |
| showEvent | A Boolean variable to control whether or not to show the number of events. By default, it is set to TRUE. |
| showDropout | A Boolean variable to control whether or not to show the number of dropouts. By default, it is set to FALSE. |
| showOngoing | A Boolean variable to control whether or not to show the number of ongoing subjects. By default, it is set to FALSE. |
| by_treatment | A Boolean variable to control whether or not to predict event by treatment group. By default, it is set to FALSE. |
| seed.num | The number of the random seed. The default is NULL. |

Details

To ensure successful event prediction at the design stage, it is important to provide the newSubjects data set.

To specify the event model used during the design-stage event prediction, the `event_fit` be a list with one element per treatment. For each treatment, the element should include `w` to specify the weight of the treatment in a randomization block, `model` to specify the event model (exponential, weibull, log-logistic, log-normal, or piecewise exponential, weibull with cured population, exponential with cured population, log-normal with cured population, log-logistic with cured population, piecewise exponential with cured population, exponential with cured population and delayed treatment, weibull with cured population and delayed treatment, log-normal with cured population and delayed treatment, log-logistic with cured population and delayed treatment), `theta` and `vtheta` to indicate the parameter values and the covariance matrix. For the piecewise exponential or piecewise exponential with cured population or piecewise exponential with cured population and delayed treatment event model, the list should also include `piecewiseSurvivalTime` to indicate the location of knots. It should be noted that the model averaging and spline options are not appropriate for use as prior.

To specify the dropout model used during the design stage event prediction, the `dropout_fit` should be a list with one element per treatment. For each treatment, the element should include `w` to specify the weight of the treatment in a randomization block, `model` to specify the dropout model (exponential, weibull, log-logistic, log-normal, or piecewise exponential), `theta` and `vtheta` to indicate the parameter values and the covariance matrix. For the piecewise exponential dropout model, the list should also include `piecewiseDropoutTime` to indicate the location of knots.

Following the commencement of the trial, we obtain the event model fit and the dropout model fit based on the observed data, denoted as `event_fit` and `dropout_fit`, respectively. These fitted models are subsequently utilized to generate event and dropout times for both ongoing and new subjects in the trial.

Value

A list of prediction results which includes important information such as the median, lower and upper percentiles for the estimated day and date to reach the target number of events, as well as simulated event data for both ongoing and new subjects. The data for the prediction plot is also included within this list.

References

- Bagiella, Emilia, and Daniel F. Heitjan. "Predicting analysis times in randomized clinical trials." *Statistics in medicine* 20.14 (2001): 2055-2063.
- Ying, Gui-shuang, and Daniel F. Heitjan. "Weibull prediction of event times in clinical trials." *Pharmaceutical Statistics: The Journal of Applied Statistics in the Pharmaceutical Industry* 7.2 (2008): 107-120.
- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

Examples

```
fit1 <- list(model = "piecewise uniform",
            theta = -0.58,
            vtheta=0, accrualTime =0)
fit2<-list()
fit2[[1]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(-2.2,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit2[[2]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(-2.2,0,6.5,46,0.65),
                vtheta = matrix(0,5,5))

enroll_pred <- predictEnrollment(df = NULL, target_n=200, enroll_fit = fit1,lags=46,
                                pilelevel=0.9, nyears=4, nreps=100,by_treatment=TRUE,
                                ngroups=2, alloc=c(1,1), treatment_label=c('a','b'))

event_pred <- predictEvent(df = NULL, target_d=60,
                           newSubjects = enroll_pred$newSubjects,
                           event_fit = fit2,dropout_fit = NULL,
                           pilelevel=0.9,
                           nyears=4,
                           nreps=100,
                           by_treatment=TRUE)
```

smed

Function to output summary statistics from survfit function output

Description

Provide summary statistics from survfit function output

Usage

smed(x)

Arguments

x an object returned by "survfit"

Value

"smed" returns a matrix of 5 columns of

Examples

```
n <- 500
event <- runif(n,1, 5)
osc<-1*(event<=4)
os <- pmin(event,4)

fit1<-survival::survfit(survival::Surv(os,osc)~1)
smed(fit1)
```

SP_Chen_exponential *Survival probability function of the exponential distribution with cured population*

Description

Calculate survival probability of the exponential distribution with cured population

Usage

```
SP_Chen_exponential(par, t)
```

Arguments

par a vector with two elements, where the first element denotes the logistic of the proportion of the cured population, and the second element denotes the log of the hazard rate.

t a vector with non-negative elements.

Value

Survival probability of the exponential distribution with cured population given parameters par at times t.

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." BMC medical research methodology 16.1 (2016): 1-10.

SP_Chen_log_logistic *Survival probability function of the log-logistic distribution with cured population*

Description

Calculate survival probability of the log-logistic distribution with cured population

Usage

```
SP_Chen_log_logistic(par, t)
```

Arguments

| | |
|-----|---|
| par | a vector with three elements, where the first element denotes the logistic of the proportion of the cured population, and the second element and the third element denote the log of shape and the log of the scale parameter of the log-logistic distribution. |
| t | a vector with non-negative elements. |

Value

Survival probability of the log-logistic distribution with cured population given parameters par at times t.

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." BMC medical research methodology 16.1 (2016): 1-10.

SP_Chen_log_normal *Survival probability function of the log-normal distribution with cured population*

Description

Calculate survival probability of the log-normal distribution with cured population

Usage

```
SP_Chen_log_normal(par, t)
```

Arguments

- `par` a vector with three elements, where the first element denotes the logistic of the proportion of the cured population, and the second element and the third element denote the mean and the log of standard deviation parameter of the log-normal distribution.
- `t` a vector with non-negative elements.

Value

Survival probability of the log-normal distribution with cured population given parameters `par` at times `t`.

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.
- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

SP_Chen_piecewise_exponential

Survival probability function of the piecewise exponential distribution with cured population

Description

Calculate survival probability of the piecewise exponential distribution with cured population

Usage

```
SP_Chen_piecewise_exponential(par, t, piecewiseSurvivalTime)
```

Arguments

- `par` a vector with $m+1$ elements, where the first element denotes the logistic of the proportion of the cured population, and the rest element denotes the log of the hazard rate in intervals
- `t` a vector with non-negative elements.
- `piecewiseSurvivalTime`
A vector that specifies the time intervals for the piecewise exponential survival distribution. Must start with 0, e.g., `c(0, 60)` breaks the time axis into 2 event intervals: `[0, 60)` and `[60, Inf)`. By default, it is set to 0.

Value

Survival probability of the piecewise-exponential distribution with cured population given parameters `par` at times `t`.

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

| | |
|-----------------|--|
| SP_Chen_weibull | <i>Survival probability function of the Weibull distribution with cured population</i> |
|-----------------|--|

Description

Calculate survival probability of the Weibull distribution with cured population

Usage

```
SP_Chen_weibull(par, t)
```

Arguments

| | |
|-----|--|
| par | a vector with three elements, where the first element denotes the logistic of the proportion of the cured population, and the second element and the third element denote the log of the shape and log of the scale parameter of the Weibull distribution. |
| t | a vector with non-negative elements. |

Value

Survival probability of the Weibull distribution with cured population given parameters par at times t.

References

- Chen, Tai-Tsang. "Predicting analysis times in randomized clinical trials with cancer immunotherapy." *BMC medical research methodology* 16.1 (2016): 1-10.

| | |
|-------------------|--------------------------------|
| summarizeObserved | <i>Summarize observed data</i> |
|-------------------|--------------------------------|

Description

Provides an overview of the observed data, including the trial start date, data cutoff date, enrollment duration, number of subjects enrolled, number of events and dropouts, number of subjects at risk, cumulative enrollment and event data, daily enrollment rates, and Kaplan-Meier plots for time to event and time to dropout.

Usage

```
summarizeObserved(
  df,
  to_predict = "event only",
  showplot = TRUE,
  by_treatment = FALSE
)
```

Arguments

| | |
|--------------|--|
| df | The subject-level data, including trialsdt, usubjid, randdt, and cutoffdt for enrollment prediction, as well as time, event and dropout for event prediction, and treatment coded as 1, 2, and so on, and treatment_description for prediction by treatment group. |
| to_predict | Specifies what to predict: "enrollment only", "event only", or "enrollment and event". By default, it is set to "event only". |
| showplot | A Boolean variable to control whether or not to show the observed data plots. By default, it is set to TRUE. |
| by_treatment | A Boolean variable to control whether or not to summarize observed data by treatment group. By default, it is set to FALSE. |

Value

A list that includes a range of summary statistics, data sets, and plots depending on the value of to_predict.

Examples

```
observed1 <- summarizeObserved(df = interimData1,
                               to_predict = "enrollment and event")
```

test_plot

Function to plot KM plot for time-to-event data in simulation

Description

Plot KM plot for each arm at one realization

Usage

```
test_plot(test0, plot.index = 1)
```

Arguments

| | |
|------------|--|
| test0 | an object obtained from test_procedure |
| plot.index | the index of simulation |

Value

A KM plot for events in each arm

Examples

```
fit1 <- list(model = "piecewise uniform",
            theta = -0.58,
            vtheta=0, accrualTime =0)
fit2<-list()
fit2[[1]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(0.5,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit2[[2]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(0.5,0,6.5,46,0.65),
                vtheta = matrix(0,5,5))
fit3<-list()
fit3[[1]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(0.5,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit3[[2]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(0.5,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit4 <- list(model = "exponential",
            theta =log(0.0003),
            vtheta=0)

test1<-test_procedure(pilevel=0.9,nyears=4,enroll_fit=fit1,
                    dropout_fit=fit4,enroll_prior=fit1,event_prior_h0=fit3,
                    event_prior_ha=fit2,dropout_prior=NULL,
                    target_n=200,target_IA_d=40,
                    target_d=60,ialpha=0.016,falpha=0.0450,
                    lag=46,by_fitted_enroll=FALSE,
                    by_fitted_dropout=FALSE,treatment_label=c('a','b'),
                    ngroups=2,alloc=c(1,1),nreps=10, IA_included=TRUE)

test_plot(test1)
```

test_procedure

Function to provide summary and test statistics based on simulation.

Description

Provides summary and test statistics based on simulation.

Usage

```
test_procedure(
  pilevel = 0.9,
  nyears = 4,
```

```

enroll_fit = enroll_fit,
dropout_fit = dropout_fit,
enroll_prior = NULL,
event_prior_h0 = NULL,
event_prior_ha = NULL,
dropout_prior = NULL,
target_n,
target_IA_d,
target_d,
ialpha = 0.025,
falpha,
lag,
by_fitted_enroll = FALSE,
by_fitted_dropout = FALSE,
treatment_label,
ngroups = 2,
alloc = NULL,
nreps = 500,
IA_included,
test = "Superiority",
test_IA = "Superiority",
Futility_boundary = 1,
seed.num = NULL
)

```

Arguments

| | |
|------------------|--|
| pilevel | the confidence interval, the default is 0.95. |
| nyears | the year after data cutoff or follow-up. |
| enroll_fit | an object generated from fitEnrollment. |
| dropout_fit | an object generated from fitDropout. |
| enroll_prior | The prior of enrollment model parameters. |
| event_prior_h0 | The prior of event model parameters under null hypothesis |
| event_prior_ha | The prior of event model parameters under alternative hypothesis |
| dropout_prior | The prior of dropout model parameters. |
| target_n | The target number of subjects to enroll in the study. |
| target_IA_d | number of events needed for interim analysis |
| target_d | number of events needed for primary analysis |
| ialpha | interim analysis alpha nominal value (only one interim allowed) |
| falpha | primary analysis alpha nominal value |
| lag | a scalar to denote time (days). Hazard ratio before and after this time would be calculated. |
| by_fitted_enroll | A Boolean variable to control whether or not to predict enrollment time with fitted model. By default, it is set to FALSE. |

| | |
|-------------------|---|
| by_fitted_dropout | A Boolean variable to control whether or not to predict dropout time with fitted model. By default, it is set to FALSE. |
| treatment_label | The treatment labels for treatments in a randomization block for design stage prediction. |
| ngroups | The number of treatment groups for enrollment prediction at the design stage. By default, it is set to 2. It is replaced with the actual number of treatment groups in the observed data if df is not NULL. |
| alloc | The treatment allocation in a randomization block. By default, it is set to NULL, which yields equal allocation among the treatment groups. |
| nreps | The number of replications for simulation. By default, it is set to 500. |
| IA_included | A Boolean variable to control whether or not to include one interim analysis. By default, it is set to FALSE. |
| test | a character denotes the test type, includes "Superiority", "Futility", "Two-sided" |
| test_IA | a character denotes the test type in interim analysis, includes "Efficacy", "Futility", or "Efficacy and Futility" |
| Futility_boundary | a positive number denotes the boundary of the Futility in the scale of hazard ratio |
| seed.num | The number of the random seed. The default is NULL. |

Value

A list with following components

- iteration0 - the number of simulations that achieved target number of events in interim analysis and primary analysis under null hypothesis.
- iteration1 - the number of simulations that achieved target number of events in interim analysis and primary analysis under alternative hypothesis.
- simu_summary - the summary table of number of simulations that achieved or do not achieve target number of events in each analysis under null hypothesis and alternative hypothesis.
- power - the alpha and powers from log-rank test and Fleming&Harrington test
- samplesize - the counts per arm and total, includes the number of patients, events at interim analysis and primary analysis, events at interim analysis before delay, events at primary analysis before delay
- hzratio - average hazard ratio at primary analysis and interim analysis
- hzrc - Frequencies of hazard ratios in specific zones
- hzratio2 - HR before and after delay
- median - Medians of survival time at interim analysis and primary analysis
- osrate - survival rate at milestones (1, 2 and 4 years)
- duration - Study duration for enrollment, interim analysis and primary analysis
- duration1 - Durations for interim analysis and primary analysis with 95% CI

- textH0 - the summary text of number of simulations that achieved or do not achieve target number of events in primary analysis under null hypothesis.
- textHA - the summary text of number of simulations that achieved or do not achieve target number of events in primary analysis under alternative hypothesis.

Examples

```
fit1 <- list(model = "piecewise uniform",
            theta = -0.58,
            vtheta=0, accrualTime =0)
fit2<-list()
fit2[[1]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(-2.2,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit2[[2]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(-2.2,0,6.5,46,0.65),
                vtheta = matrix(0,5,5))
fit3 <-list()
fit3[[1]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(-2.2,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit3[[2]] <- list(model = "weibull with cured population and delayed treatment",
                theta = c(-2.2,0,6.5,0,1),
                vtheta = matrix(0,5,5))
fit4 <-list()
fit4[[1]] <- list(model = "exponential",
                theta =log(0.0003),
                vtheta=0)
fit4[[2]] <- list(model = "exponential",
                theta =log(0.0003),
                vtheta=0)
test1<-test_procedure(pilevel=0.9,nyears=4,enroll_fit=fit1,
                    dropout_fit=fit4,enroll_prior=fit1,event_prior_h0=fit3,
                    event_prior_ha=fit2,dropout_prior=NULL,
                    target_n=200,target_IA_d=40,target_d=60,
                    ialpha=0.016,falpha=0.0450,
                    lag=46,by_fitted_enroll=FALSE,
                    by_fitted_dropout=FALSE,treatment_label=c('a','b'),
                    ngroups=2,alloc=c(1,1),nreps=100, IA_included=TRUE)
```

 tte

Calculating log-rank test p-value, median time from each arm, hazard ratio between two arms, number of subjects and events in time-to-event outcomes.

Description

Calculate log-rank test p-value, median time from each arm, HR between arms, number of subjects and events

Usage

```
tte(os, osc, grp, type, test = "Futility")
```

Arguments

| | |
|------|---|
| os | Time to event variable |
| osc | Time to event censoring variable |
| grp | Treatment assignment indicator with 1 denoting the treated group, and 0 denoting the placebo group. |
| type | either "all" or "logrank" or "hr" |
| test | a character denotes the test type, include "Superiority", "Futility", "Two-sided" |

Details

The control arm

Value

If type='all', return a list that includes the log-rank p-value, median time from each arm, hazard ratio between arms, and 95% confidence interval of hazard ratio, number of subjects and events; and events If type='logrank', return a list that includes the log-rank p-value, number of subjects and events; If type='hr', return a list that includes hazard ratio between arms, and 95% confidence interval of hazard ratio

Examples

```
n <- 500
event <- runif(n,1, 5)
osc<-1*(event<=4)
os <- pmin(event,4)
trt<-c(rep(0,n/2),rep(1,n/2))
tte(os,osc,trt,type='all')
```

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