Package ‘DTEAssurance’

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Type Package

Title Assurance Methods for Clinical Trials with a Delayed Treatment Effect

Version 1.0.0

Description Provides functions for planning clinical trials subject to a delayed treatment effect using assurance-based methods. Includes two 'shiny' applications for interactive exploration, simulation, and visualisation of trial designs and outcomes. The methodology is described in:
Salsbury JA, Oakley JE, Julious SA, Hampson LV (2024)
``Assurance methods for designing a clinical trial with a delayed treatment effect'' <doi:10.1002/sim.10136>,
Salsbury JA, Oakley JE, Julious SA, Hampson LV (2024)
``Adaptive clinical trial design with delayed treatment effects using elicited prior distributions'' <doi:10.48550/arXiv.2509.07602>.

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Contents

add_recruitment_time *Add recruitment time to a survival dataset*

Description

Simulates recruitment timing for each subject in a survival dataset using either a power model or a piecewise constant (PWC) model. The function appends recruitment times and pseudo survival times (time from recruitment to event or censoring).

Usage

```
add_recruitment_time(
  data,
  rec_method,
  rec_period = NULL,
  rec_power = NULL,
  rec_rate = NULL,
  rec_duration = NULL
)
```

Arguments

`data`	A dataframe containing survival data with columns: `time`, `status`, and `group`
`rec_method`	Recruitment method: `"power"` for power model or `"PWC"` for piecewise constant model
`rec_period`	Period length for the power model
`rec_power`	Power parameter for the power model
`rec_rate`	Comma-separated string of recruitment rates for the PWC model
`rec_duration`	Comma-separated string of durations corresponding to each rate in the PWC model

Value

A dataframe with two additional columns:

rec_time Simulated recruitment time for each subject

pseudo_time Time from recruitment to event or censoring

Class: `data.frame`

Examples

```
set.seed(123)
df <- data.frame(
  time = rexp(20, rate = 0.1),
  status = rbinom(20, 1, 0.8),
  group = rep(c("Control", "Treatment"), each = 10)
)
recruited <- add_recruitment_time(df, rec_method = "power", rec_period = 12, rec_power = 1)
head(recruited)
```

---

assurance_GSD_shiny_app

Launch the 'shiny' GSD Assurance app

Description

Launches a 'shiny' application to simulate group sequential trials with delayed treatment effects (DTE) using elicited prior distributions. The app allows interactive exploration of trial designs and assurance calculations.

Usage

```
assurance_GSD_shiny_app()
```

Value

No return value, called for side effects (invisibly returns NULL). The function launches an interactive 'shiny' application.

Examples

```
if (interactive()) {
  # Launch the interactive app in an R session
  assurance_GSD_shiny_app()
}
```

assurance_shiny_app *Launch the 'shiny' Assurance app*

Description

Launches a 'shiny' application to calculate assurance for clinical trials where delayed treatment effects (DTE) may be present. The app allows elicitation of prior distributions and calculates assurance metrics.

Usage

```
assurance_shiny_app()
```

Value

No return value, called for side effects (invisibly returns NULL). The function launches an interactive 'shiny' application.

Examples

```
if (interactive()) {
  # Launch the interactive app in an R session
  assurance_shiny_app()
}
```

calc_dte_assurance *Calculate Assurance for a Trial with a Delayed Treatment Effect*

Description

Simulates operating characteristics for a clinical trial under prior uncertainty about a delayed treatment effect. The function integrates beliefs about control survival, treatment delay, post-delay hazard ratio, recruitment, censoring, and analysis method to estimate assurance and other trial metrics.

Usage

```
calc_dte_assurance(
  n_c,
  n_t,
  control_model,
  effect_model,
  censoring_model,
  recruitment_model,
  analysis_model,
  n_sims = 1000
)
```

Arguments

`n_c` Vector of control group sample sizes

`n_t` Vector of treatment group sample sizes

`control_model` A named list specifying the control arm survival distribution:

- `dist`: Distribution type ("Exponential" or "Weibull")
- `parameter_mode`: Either "Fixed" or "Distribution"
- `fixed_type`: If "Fixed", specify as "Parameters" or "Landmark"
- `lambda`, `gamma`: Scale and shape parameters
- `t1`, `t2`: Landmark times
- `surv_t1`, `surv_t2`: Survival probabilities at landmarks
- `t1_Beta_a`, `t1_Beta_b`, `diff_Beta_a`, `diff_Beta_b`: Beta prior parameters

`effect_model` A named list specifying beliefs about the treatment effect:

- `delay_SHELF`, `HR_SHELF`: SHELF objects encoding beliefs
- `delay_dist`, `HR_dist`: Distribution types ("hist" by default)
- `P_S`: Probability that survival curves separate
- `P_DTE`: Probability of delayed separation, conditional on separation

`censoring_model`

A named list specifying the censoring mechanism:

- `method`: "Time", "Events", or "IF"
- `time`, `events`, `IF`: Parameters for each method

`recruitment_model`

A named list specifying the recruitment process:

- `method`: "power" or "PWC"
- `period`, `power`: Parameters for power model
- `rate`, `duration`: Comma-separated strings for PWC model

`analysis_model` A named list specifying the statistical test and decision rule:

- `method`: "LRT", "WLRT", or "MW"
- `alpha`, `alternative_hypothesis`: Type I error and hypothesis direction
- `rho`, `gamma`, `t_star`, `s_star`: Parameters for WLRT or MW
- `success_threshold_HR`: Optional threshold for declaring success

`n_sims` Number of simulations to run (default = 1000)

Value

A named list containing:

assurance Estimated assurance (probability of success under prior uncertainty)

CI 95% confidence interval for assurance

duration Mean trial duration across simulations

sample_size Mean sample size across simulations

diagnostics Additional diagnostics if `success_threshold_HR` is specified

Class: `list`

Examples

```
# Minimal example with placeholder inputs
control_model <- list(dist = "Exponential", parameter_mode = "Fixed",
fixed_type = "Parameters", lambda = 0.1)
effect_model <- list(delay_SHELF = SHELF::fitdist(c(3, 4, 5),
probs = c(0.25, 0.5, 0.75), lower = 0, upper = 10),
delay_dist = "gamma",
HR_SHELF = SHELF::fitdist(c(0.55, 0.6, 0.7), probs = c(0.25, 0.5, 0.75), lower = 0, upper = 1.5),
HR_dist = "gamma",
P_S = 1, P_DTE = 0)
censoring_model <- list(method = "Time", time = 12)
recruitment_model <- list(method = "power", period = 12, power = 1)
analysis_model <- list(method = "LRT", alpha = 0.025, alternative_hypothesis = "two.sided")
result <- calc_dte_assurance(n_c = 300, n_t = 300,
                                     control_model = control_model,
                                     effect_model = effect_model,
                                     censoring_model = censoring_model,
                                     recruitment_model = recruitment_model,
                                     analysis_model = analysis_model,
                                     n_sims = 10)
str(result)
```

---

calc_dte_assurance_interim

Calculates operating characteristics for a Group Sequential Trial with a Delayed Treatment Effect

---

Description

Simulates assurance and operating characteristics for a group sequential trial under prior uncertainty about a delayed treatment effect. The function integrates beliefs about control survival, treatment delay, post-delay hazard ratio, recruitment, and group sequential design (GSD) parameters.

Usage

```
calc_dte_assurance_interim(
  n_c,
  n_t,
  control_model,
  effect_model,
  recruitment_model,
  GSD_model,
  n_sims = 1000
)
```

Arguments

`n_c` Control group sample size

`n_t` Treatment group sample size

`control_model` A named list specifying the control arm survival distribution:

- `dist`: Distribution type ("Exponential" or "Weibull")
- `parameter_mode`: Either "Fixed" or "Distribution"
- `fixed_type`: If "Fixed", specify as "Parameters" or "Landmark"
- `lambda`, `gamma`: Scale and shape parameters
- `t1`, `t2`: Landmark times
- `surv_t1`, `surv_t2`: Survival probabilities at landmarks
- `t1_Beta_a`, `t1_Beta_b`, `diff_Beta_a`, `diff_Beta_b`: Beta prior parameters

`effect_model` A named list specifying beliefs about the treatment effect:

- `delay_SHELF`, `HR_SHELF`: SHELF objects encoding beliefs
- `delay_dist`, `HR_dist`: Distribution types ("hist" by default)
- `P_S`: Probability that survival curves separate
- `P_DTE`: Probability of delayed separation, conditional on separation

`recruitment_model` A named list specifying the recruitment process:

- `method`: "power" or "PWC"
- `period`, `power`: Parameters for power model
- `rate`, `duration`: Comma-separated strings for PWC model

`GSD_model` A named list specifying the group sequential design:

- `events`: Total number of events
- `alpha_spending`: Cumulative alpha spending vector
- `beta_spending`: Cumulative beta spending vector
- `IF_vec`: Vector of information fractions

`n_sims` Number of simulations to run (default = 1000)

Value

A data frame with one row per simulated trial and the following columns:

Trial Simulation index

IF Information fraction label used at the decision point

Decision Interim decision outcome (e.g., "Continue", "Stop for efficacy", "Stop for futility")

StopTime Time at which the trial stopped or completed

SampleSize Total sample size at the time of decision

Final_Decision Final classification of trial success based on the test statistic and threshold

Class: `data.frame`

Examples

```
# Minimal example with placeholder inputs
control_model <- list(dist = "Exponential", parameter_mode = "Fixed",
fixed_type = "Parameters", lambda = 0.1)
effect_model <- list(P_S = 1, P_DTE = 0,
HR_SHELF = SHELF::fitdist(c(0.6, 0.65, 0.7), probs = c(0.25, 0.5, 0.75), lower = 0, upper = 2),
HR_dist = "gamma",
delay_SHELF = SHELF::fitdist(c(3, 4, 5), probs = c(0.25, 0.5, 0.75), lower = 0, upper = 10),
delay_dist = "gamma"
)
recruitment_model <- list(method = "power", period = 12, power = 1)
GSD_model <- list(events = 300, alpha_spending = c("0.01, 0.025"),
                  beta_spending = c("0.05, 0.1"), IF_vec = c("0.5, 1"))
result <- calc_dte_assurance_interim(n_c = 300, n_t = 300,
                        control_model = control_model,
                        effect_model = effect_model,
                        recruitment_model = recruitment_model,
                        GSD_model = GSD_model,
                        n_sims = 10)
str(result)
```

`cens_data` *Censor a survival dataset*

Description

Applies administrative censoring to a survival dataset using one of three methods: fixed time, fixed number of events, or fixed information fraction. The input data must contain columns for pseudo survival time, recruitment time, and observed time.

Usage

```
cens_data(
  data,
  cens_method = "Time",
  cens_time = NULL,
  cens_IF = NULL,
  cens_events = NULL
)
```

Arguments

`data`	A dataframe containing uncensored survival data with columns: `pseudo_time`, `rec_time`, and `time`
`cens_method`	Censoring method: `"Time"` (default), `"Events"`, or `"IF"`
`cens_time`	Time point for censoring (required if `cens_method` = `"Time"`)
`cens_IF`	Information fraction for censoring (required if `cens_method` = `"IF"`)
`cens_events`	Number of events for censoring (required if `cens_method` = `"Events"`)

Value

A list containing:

data Censored dataframe with updated `status` and filtered rows

cens_events Number of events used for censoring (if applicable)

cens_time Time point used for censoring

sample_size Number of subjects remaining after censoring

Examples

```
set.seed(123)
df <- data.frame(
  pseudo_time = rexp(20, rate = 0.1),
  rec_time = runif(20, 0, 12),
  time = rexp(20, rate = 0.1)
)
censored <- cens_data(df, cens_method = "Time", cens_time = 10)
str(censored)
```

`INTEREST` *INTEREST data set*

Description

A reconstructed survival data set for the INTEREST clinical trial

Usage

```
INTEREST
```

Format

A data frame with 710 rows and 2 variables:

Survival time Survival Time (in months)

Status Event indicator (0=Alive, 1=Dead)

Source

Reconstructed survival data set from the following publication: https://www.sciencedirect.com/science/article/pii/S01406736

`MCMC_sample` *MCMC_sample*

Description

An MCMC sample for the example given in Salsbury et al (2024)

Usage

```
MCMC_sample
```

Format

A data frame with 100000 rows and 1 variables:

x Sample from the MAP prior

Source

A MCMC sample for the control group for the example given in https://onlinelibrary.wiley.com/doi/full/10.1002/sim.10136. Three historical data seta are used to generate a Meta-Analytic-Predictive Prior distribution

`REVEL` *REVEL data set*

Description

A reconstructed survival data set for the REVEL clinical trial

Usage

```
REVEL
```

Format

A data frame with 625 rows and 2 variables:

Survival time Survival Time (in months)

Status Event indicator (0=Alive, 1=Dead)

Source

Reconstructed survival data set from the following publication: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)60845-X/fulltext

`sim_dte`	*Simulates survival times for a delayed treatment effect (DTE) scenario, where the treatment group experiences a delayed onset of benefit. Control and treatment groups are generated under exponential or Weibull distributions.*

Description

Simulates survival times for a delayed treatment effect (DTE) scenario, where the treatment group experiences a delayed onset of benefit. Control and treatment groups are generated under exponential or Weibull distributions.

Usage

```
sim_dte(
  n_c,
  n_t,
  lambda_c,
  delay_time,
  post_delay_HR,
  dist = "Exponential",
  gamma_c = NULL
)
```

Arguments

`n_c`	The number of patients in the control group
`n_t`	The number of patients in the treatment group
`lambda_c`	The baseline hazard rate for the control group
`delay_time`	The length of delay before treatment effect begins
`post_delay_HR`	The hazard ratio after the delay period
`dist`	The distribution for the control group; must be one of "Exponential" (default) or "Weibull"
`gamma_c`	The shape parameter for the Weibull distribution (only used if `dist = "Weibull"`)

Value

A data frame with two columns:

`time`	Simulated survival times
`group`	Group assignment: "Control" or "Treatment"

Class: `data.frame`

Examples

```
set.seed(123)
sim_data <- sim_dte(n_c = 10, n_t = 10, lambda_c = 0.1,
                    delay_time = 6, post_delay_HR = 0.6)
head(sim_data)
```

---

survival_test *Calculate statistical significance on a survival dataset*

Description

Performs a survival analysis using either the standard log-rank test (LRT) or a weighted log-rank test (WLRT). The function estimates the hazard ratio and determines whether the result is statistically significant based on the specified alpha level and alternative hypothesis.

Usage

```
survival_test(
  data,
  analysis_method = "LRT",
  alternative = "one.sided",
  alpha = 0.05,
  rho = 0,
  gamma = 0,
  t_star = NULL,
  s_star = NULL
)
```

Arguments

`data` A dataframe containing survival data. Must include columns for survival time, event status, and treatment group.

`analysis_method` Method of analysis: "LRT" (default) for standard log-rank test, or "WLRT" for weighted log-rank test.

`alternative` String specifying the alternative hypothesis. Must be one of "one.sided" or "two.sided" (default).

`alpha` Type I error threshold for significance testing.

`rho` Rho parameter for the Fleming-Harrington weighted log-rank test.

`gamma` Gamma parameter for the Fleming-Harrington weighted log-rank test.

`t_star` Parameter t^* used in modestly weighted tests.

`s_star` Parameter s^* used in modestly weighted tests.

Value

A list containing:

Signif Logical indicator of statistical significance based on the chosen test and alpha level.

observed_HR Estimated hazard ratio from a Cox proportional hazards model.

Examples

```
set.seed(123)
df <- data.frame(
  survival_time = rexp(40, rate = 0.1),
  status = rbinom(40, 1, 0.8),
  group = rep(c("Control", "Treatment"), each = 20)
)
result <- survival_test(df, analysis_method = "LRT", alpha = 0.05)
str(result)
```

`ZODIAC` *ZODIAC data set*

Description

A reconstructed survival data set for the ZODIAC clinical trial

Usage

```
ZODIAC
```

Format

A data frame with 697 rows and 2 variables:

Survival time Survival Time (in months)

Status Event indicator (0=Alive, 1=Dead)

Source

Reconstructed survival data set from the following publication: https://www.sciencedirect.com/science/article/abs/pii/S14702

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