Package ‘RTSA’

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Type Package
Title 'Trial Sequential Analysis' for Error Control and Inference in Sequential Meta-Analyses
Version 0.1.0
Description Frequentist meta-analysis and sequential meta-analysis based on 'Trial Sequential Analysis' (TSA) by Copenhagen Trial Unit (CTU). Primary usage is the calculation of group sequential designs for meta-analysis to be used for planning and analysis of both prospective and retrospective sequential meta-analyses to preserve type-I-error control under sequential testing. 'RTSA' includes tools for sample and trial size calculation for meta-analysis and core meta-analyses methods such as fixed-effect and random-effects models and forest plots. TSA is described in Wetterslev et. al (2008) <doi:10.1016/j.jclinepi.2007.03.013>. The methods for deriving the group sequential designs are based on Jennison and Turnbull (1999, ISBN:9780849303166).
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**Description**

Calculates alpha- and potentially beta-spending boundaries for group sequential designs for meta-analysis together with a scalar to achieve the wanted level of power.

**Usage**

```r
boundaries(
  timing,
  alpha,
  beta,
  side,
  futility = "none",
  es_alpha,
  es_beta = NULL,
  tol = 1e+09,
  type = "design",
  design_R = NULL
)
```

**Arguments**

- `timing` Expected timings of interim analyses and final analysis.
- `alpha` The level of type I error
- `beta` The level of type II error
- `side` Whether a 1- or 2-sided hypothesis test is used. Options are 1 or 2.
- `futility` Futility boundaries added to design. Options are: none, non-binding and binding. Default is "none".
The spending function for alpha-spending. Options are: "esOF" (Lan & DeMets version of O'Brien-Fleming), "esPoc" (Lan & DeMets version of Pocock), "HSDC" (Hwang Sihi and DeCani) and "rho" (rho family).

The spending function for beta-spending. For options see es_alpha.

Tolerance level.

Whether the boundaries are used for design or analysis. Defaults to design.

If type is analysis, a scalar for achieving the right amount of power must be provided.

A boundaries object which includes:

- `inf_frac`: Timing of interim analyses and final analysis. Potentially modified if type = "analysis".
- `org_inf_frac`: Original timing. If type = "design" NULL.
- `alpha_ubound`: Upper alpha-spending boundaries
- `alpha_lbound`: Lower alpha-spending boundaries
- `alpha`: As input
- `alpha_spend`: List of cumulative and incremental spending
- `delta`: Drift parameter
- `design_R`: If type = "analysis" it is the scalar for correct power in the design. Else NULL.
- `info`: List of the information as the squareroot of the information increments and the squareroot of the cumulative information
- `beta_ubound`: Upper beta-spending boundaries
- `beta_lbound`: Lower beta-spending boundaries
- `root`: Scalar for achieving correct power
- `beta_spend`: List of cumulative and incremental spending
- `pwr`: List of probabilities for rejecting the null under the sample size settings being true at each analysis and the sum
- `tIe`: List of probabilities for type-I-error at each analysis and the sum
- `side`: As input
- `beta`: As input
- `es_alpha`: As input
- `es_beta`: As input
- `type`: As input
- `futility`: As input

Examples

```r
boundaries(timing = c(0.25, 0.5, 0.75, 1), alpha = 0.05, beta = 0.1, side = 2, futility = "non-binding", es_alpha = "esOF", es_beta = "esOF")
```
**coronary**

*Description*

A dataset containing data on ...

*Usage*

coronary

*Format*

A data frame with 6 rows and 5 variables:

- **study**  Name of first author of the trial
- **eI**   Number of events in the intervention group
- **nI**   Number of pax in the intervention group
- **eC**   Number of events in the control group
- **nC**   Number of pax in the control group

**eds**

*Description*

A dataset containing data on the length of hospital stay when receiving early supported discharge (ESD) service versus conventional care. The outcome is length of initial hospital stay counted in days.

*Usage*

eds

*Format*

A data frame with 9 studies and 8 variables:
Details

- study. Name of the city of the study
- year. Year of the trial
- mI. Mean duration at hospital in intervention (ESD) group
- mC. Mean duration at hospital in control group
- sdl. Standard deviation of intervention (ESD) estimate
- sdC. Standard deviation of control estimate
- nI. Number of participants in the intervention (ESD) group
- nC. Number of participants in the control group

References


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\textit{inference} \quad I_{\text{nference from RTSA}}

Description

Naive inference, TSA-adjusted confidence intervals and stage-wise ordered inference if the meta-analysis crosses a alpha-spending boundary or a binding beta-spending boundary.

Usage

\begin{verbatim}
inference(
    design, timing, ana_time, ma, fixed, conf_int = "sw", conf_level = 0.95, direction, tol = 1e-15
  )
\end{verbatim}

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>design</td>
<td>design</td>
</tr>
<tr>
<td>timing</td>
<td>timing</td>
</tr>
<tr>
<td>ana_time</td>
<td>analysis times</td>
</tr>
<tr>
<td>ma</td>
<td>meta-analysis item</td>
</tr>
</tbody>
</table>
metaanalysis

Fixed-effect or random-effects meta-analysis

Description

Computes a fixed-effect or random-effects meta-analysis including heterogeneity statistics. If `mc` is specified, a retrospective sample and trial size is calculated.

Usage

```r
metaanalysis(
  outcome,
  data,
  study = NULL,
  side = 2,
  weights = "IV",
  fixed = TRUE
)
```

### Arguments

- **outcome**: A character string indicating the outcome of interest.
- **data**: A data frame containing the data for the meta-analysis.
- **study**: An optional character string indicating the study.
- **side**: An integer indicating whether to use a one-sided or two-sided test. Use `2` for two-sided and `1` for one-sided.
- **weights**: A character string indicating the type of weighting to be used. Options include `"IV"` for inverse variance, `"Peto"` for Peto, and `"Mantel-Haenszel"` for Mantel-Haenszel.
- **fixed**: A logical value indicating whether to perform a fixed-effect or random-effects meta-analysis. Use `TRUE` for fixed-effect and `FALSE` for random-effects.
metaanalysis

```r
cont_vartype = "equal",
alpha = 0.05,
beta = 0.1,
re_method = "DL",
tau_ci_method = "BJ",
mc = NULL,
sd_mc = NULL,
zero_adj = 0.5,
...
```

Arguments

- **outcome**: Outcome metric for the studies. Choose between: MD (mean difference), RR (relative risk), RD (risk difference) or OR (odds ratio).
- **data**: A data.frame containing the study results. The data set must containing a specific set of columns. These are respectively 'eI' (events in intervention group), 'eC' (events in control group), 'nC' (participants intervention group) or 'nI' (participants control group) for discrete data, or, 'mI' (mean intervention group), 'mC' (mean control group), 'sdI' (standard error intervention group), 'sdC' (standard error control group), 'nC' (participants intervention group) and 'nI' (participants control group) for continuous outcomes. Preferable also a 'study' column as an indicator of study.
- **study**: Optional vector of study IDs. If no study indicator is provided in 'data', a vector of study indicators e.g. names.
- **side**: Whether a 1- or 2-sided hypothesis test is used. Options are 1 or 2. Defaults to 2.
- **weights**: Method for calculating weights. Options are "MH" (Mantel-Haenzel and only optional for binary data) or "IV" (Inverse variance weighting). Defaults to "IV".
- **cont_vartype**: Variance type for continuous outcomes. Choices are "equal" (homogeneity of treatment group variances) or "non-equal" (heterogeneity of treatment group variances). Defaults to "equal".
- **alpha**: Type-I-error. Defaults to 0.05.
- **beta**: Type-II-error. Not used unless a sample and trial size calculation is wanted. Defaults to 0.1.
- **re_method**: Methods are "DL" for DerSimonian-Laird or "DL_HKSJ" for DerSimonian-Laird with Hartung-Knapp-Sidik-Jonkman adjustment. Defaults to "DL".
- **tau_ci_method**: Methods for computation of confidence interval for heterogeneity estimate tau. Calls rma.uni from the metafor package. Options are "BJ" and "QP". Defaults to "BJ".
- **mc**: Minimum clinically relevant value. Used for sample and trial size calculation.
- **sd_mc**: The expected standard deviation. Used for sample and trial size calculation for mean differences.
- **zero_adj**: Zero adjustment for null events in binary data. Options for now is 0.5.
- **...**: Additional variables. See Details.
Description

Calculate minimum number of trials for wanted power in a meta-analysis with heterogeneity

Usage

```r
minTrial(
  outcome,
  mc,
  tau2,
  alpha = 0.05,
  beta = 0.2,
  side = 2,
  p0 = NULL,
  p1 = NULL,
  var_mc = NULL,
  var_random = NULL,
  trials = NULL
)
```
Arguments

- **outcome**: Metric of interest, options include only risk ratio (RR) for now
- **mc**: Minimal clinical relevant value.
- **tau2**: Heterogeneity estimate
- **alpha**: Type I error
- **beta**: Type II error
- **side**: Whether a 1- or 2-sided hypothesis test is used. Options are 1 or 2.
- **p0**: Probability of event in control group
- **p1**: Probability of event in treatment group
- **var_mc**: Variance of the estimated effect
- **var_random**: Estimated variance from the random-effects meta-analysis
- **trials**: optional number of trials.

Value

Either a number (minimum required trials) or the minimum required required trials together with a matrix of required participants per trial given different number of trials.

Examples

```r
minTrial(outcome = "RR", p0 = 0.5, mc = 0.7, tau2 = 0.05)
```

---

**perioOxy**

Dataset of RCTs investigating the effect of 80% perioperative oxygen vs. 30-35% perioperative oxygen on surgical site infection.

---

Description

A dataset containing data on seven trials which includes their number of events per treatment group, where intervention is 80% oxygen and control is 30-35% oxygen, number of participants in each treatment group and the year of the trial.

Usage

```r
perioOxy
```

Format

A data frame with 7 rows and 6 variables:

- **study**: Name of first author of the trial
- **eI**: Number of events in the intervention group (80% oxygen)
- **nI**: Number of participants in the intervention group (80% oxygen)
- **eC**: Number of events in the control group (30-35% oxygen)
- **nC**: Number of participants in the control group (30-35% oxygen)
Description

plot.boundaries

Usage

## S3 method for class 'boundaries'
plot(x, theme = "classic", ...)

Arguments

x
  boundaries object

theme
  Whether the theme is "classic" or "aussie"

...
  Other arguments to plot.boundaries

Value

Plot. Either a plot for two- or one-sided testing.

Examples

bounds <- boundaries(timing = c(0.5, 0.75, 1), alpha = 0.025, beta = 0.2,
                      side = 1, futility = "none", es_alpha = "esOF")
plot(x = bounds)

Description

plot.RTSA

Usage

## S3 method for class 'RTSA'
plot(x, model = "random", type = "classic", theme = "classic", sign = 1, ...)

plot.RTSA
Arguments

- `x`: RTSA object
- `model`: Whether a fixed- or random-effects meta-analysis should be used. Defaults to random.
- `type`: Should Z-scores (classic) or outcome values (outcome) be plotted.
- `theme`: Whether the theme is traditional TSA (classic) or modern (modern)
- `sign`: Whether the y-axis runs from -Inf to Inf, or Inf to -Inf.
- `...`: Other arguments to plot.RTSA

Value

Plot. Either a plot for two sided testing or one-sided

Examples

```r
data(perioOxy)
outRTSA <- RTSA(type = "analysis", data = perioOxy, outcome = "RR", mc = 0.8,
side = 2, alpha = 0.05, beta = 0.2, fixed = FALSE, es_alpha = "esOF")
plot(x = outRTSA)
```

---

ris

*Calculate required sample and trials size.*

Description

Calculate required sample and trials size.

Usage

```r
ris(
  outcome,
  mc,
  side = 2,
  alpha = 0.05,
  beta = 0.1,
  fixed = TRUE,
  sd_mc = NULL,
  p0 = NULL,
  p1 = NULL,
  ma = NULL,
  tau2 = NULL,
  I2 = NULL,
  D2 = NULL,
  type = "prospective",
  trials = NULL,
  ...
)
```
Arguments

outcome Choose between: "MD" (mean difference), "RR" (relative risk), "OR" (odds ratio) or "RD" (risk difference).
mc Minimum clinical relevant effect. For "OR" or "RR" set to natural scale, not log scale.
side Test type. Set to 1 or 2 depending on the test being 1- or 2-sided.
alpha Level of type-I-error. Default value is 0.05.
beta Level of type-II-error. Default value is 0.2.
fixed Should sample size be based on a fixed- or random-effects model. Defaults to TRUE.
sd_mc Standard deviation of estimated effect. Only needed when outcome = "MD".
p0 Probability of event in control group.
p1 Probability of event in treatment group.
ma An optional metaanalysis object.
tau2 The value of the heterogeneity. Use when estimating the sample size under a random effects model. If data is provided, the estimated heterogeneity is used instead.
I2 Inconsistency.
D2 Diversity.
type Prospective or retrospective sample size calculation.
trials optional number of trials for design.
... additional arguments

Value

A list of up to 6 elements:

settings A list containing the arguments provided to the ris function.
NF The total number of required participants in a fixed-effect meta-analysis if type is prospective. Contains a list if the type is retrospective, where NF is the additional required number of participants and NF_full is the total required number of participants.
NR_taus A list containing: minTrial the minimum number of trials. nPax a matrix containing four possible number of trials with the number of participants per trial and total number of participants. tau2 the estimate used for the calculation. Might contain NR_taus_l and NR_taus_u which contain the same three elements. NR_taus_l is based on the lower value in the confidence interval of tau2. NR_taus_u is based on the upper value in the confidence interval for tau2. If the type is prospective the numbers are the total required. If the type is retrospective the numbers are the additional required.
NR_D2 The total number of required participants in a random-effects meta-analysis adjusted by diversity (D2) if type is prospective. Contains a list if the type is retrospective, where NR_D2 is the additional required number of participants and NR_D2_full is the total required number of participants.
NR_I2

The total number of required participants in a random-effects meta-analysis adjusted by inconsistency (I2) if type is prospective. Contains a list if the type is retrospective, where NR_I2 is the additional required number of participants and NR_I2_full is the total required number of participants.

Examples

ris(outcome = "RR", mc = 0.8, p0 = 0.12, fixed = TRUE)

data("perioOxy")
ma <- metaanalysis(outcome = "RR", data = perioOxy, mc = 0.8, beta = 0.2)
ma$ris
ma <- metaanalysis(outcome = "RR", data = perioOxy)
ris(outcome = "RR", mc = 0.8, ma = ma, type = "retrospective", fixed = FALSE, beta = 0.2)

Description

RTSA

Usage

RTSA(
  type = "design",
  data = NULL,
  study = NULL,
  ana_time = NULL,
  timing = NULL,
  side = NULL,
  outcome = NULL,
  mc,
  sd_mc = NULL,
  p0 = NULL,
  alpha = NULL,
  beta = NULL,
  zero_adj = 0.5,
  futility = "none",
  fixed = FALSE,
  tau2 = NULL,
  I2 = NULL,
  D2 = NULL,
  weights = "IV",
  cont_vartype = "equal",
  re_method = "DL",
  tau_ci_method = "BJ",
  es_alpha = NULL,
es_beta = NULL,
gamma = NULL,
rho = NULL,
design = NULL,
design_R = NULL,
conf_int = "sw",
conf_level = 0.95,
...
}

Arguments

type
- Type of RTSA. Options are "design" or "analysis".
data
- A data.frame containing the study results. The data set must containing a specific set of columns. These are respectively 'eI' (events in intervention group), 'eC' (events in control group), 'nC' (participants intervention group) or 'nI' (participants control group) for discrete data, or, 'mI' (mean intervention group), 'mC' (mean control group), 'sdI' (standard error intervention group), 'sdC' (standard error control group), 'nC' (participants intervention group) and 'nI' (participants control group) for continuous outcomes. Preferable also a 'study' column as an indicator of study.

study
- An optional vector of study names and perhaps year of study. Defaults to NULL.

ana_time
- An optional vector of analysis times. Used if the sequential analysis is not done for all studies included in the meta-analysis.

timing
- Expected timings of interim analyses when type = "design". Defaults to NULL.

side
- Whether a 1- or 2-sided hypothesis test is used. Options are 1 or 2.

outcome
- Outcome metric. Options are: RR (risk ratio/relative risk), OR (odds ratio), RD (risk difference) and MD (mean difference).

mc
- Minimal clinical relevant outcome value

sd_mc
- The expected standard deviation. Used for sample size calculation for mean differences.

p0
- The expected probability of event in the control group. Used for sample size calculation for binary outcomes.

alpha
- The level of type I error

beta
- The level of type II error

zero_adj
- Zero adjustment. Options for now is 0.5.

futility
- Futility boundaries added to design. Options are: none, non-binding and binding. Default is "none".

fixed
- Should only a fixed-effect meta-analysis be computed. Default is FALSE.

tau2
- Heterogeneity estimate. Used for sample and trial size calculation. Defaults to NULL.

I2
- Inconsistency estimate. Used for sample and trial size calculation. Defaults to NULL.
D2 Diversity estimate. Used for sample and trial size calculation. Defaults to NULL.

weights Weighting method options include IV (inverse-variance) and MH (Mantel-Haenszel). Defaults to IV.

cont_vartype For mean difference outcomes, do we expect the variance in the different groups to be "equal" or "non-equal".


tau_ci_method Method for calculating confidence intervals for the estimated heterogeneity tau^2. Options are "QP" for Q-profiling and "BJ" for Biggelstaff ....

es_alpha The spending function for alpha-spending. Options are: esOF (Lan & DeMets version of O'Brien-Fleming), esPoc (Lan & DeMets version of Pocock), HSDC (Hwang Sihi and DeCani) and rho (rho family).

es_beta The spending function for beta-spending. For options see es_alpha.

gamma Parameter for the HSDC error spending function.

rho Parameter for the rho family error spending function.

design RTSA object where type is design.

design_R Numerical value. The fraction used to achieve correct power. Based on sequential design.

conf_int Stopping time confidence interval. Options for now is sw (stage-wise).

conf_level Confidence level on stopping time confidence interval.

... other arguments

Value

A RTSA object, a list of five elements:

settings A list containing all of the settings used in the RTSA call. See Arguments.

ris List containing sample and trial size calculations. See documentation for ris function.

bounds List of stopping boundaries, timing of trials and more. See documentation for boundaries function.

results List of 3 to 7 elements. DARIS diversity adjusted required information size. DARIS_F fixed-effect meta-analysis required sample size. AIS Achieved information size. results_df a data.frame of inference, see documentation for inference function. seq_inf a list of conditional inference, see documentation for inference function. metaanalysis A metaanalysis object, see documentation for metaanalysis function. design_df a data.frame containing the stopping boundaries and timings from the design.

warnings List of warnings
Examples

data(perioOxy)
RTSA(type = "analysis", data = perioOxy, outcome = "RR", mc = 0.8, side = 2,
       alpha = 0.05, beta = 0.2, es_alpha = "esOF")
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