

Package ‘metaRMST’

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Title Meta-Analysis of RMSTD

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Description

R implementation of a multivariate meta-analysis model for the difference in restricted mean survival times (RMST). Use this package with individual patient level data for a time-to-event outcome to determine combined effect estimates according to 4 methods: 1) a univariate meta-analysis using observed treatment effects, 2) a univariate meta-analysis using effects predicted by fitted Royston-Parmar flexible parametric models, 3) multivariate meta-analysis with analytically derived covariance, 4) multivariate meta-analysis with bootstrap derived covariance. This package computes all combined effects and provides an RMSTD curve with option to include combined effect point estimates and their confidence intervals.

Depends R (>= 3.4.4), rstpm2

Imports mvmeta, meta, survival, survRM2, graphics

License GPL-2

Encoding UTF-8

LazyData true

RoxygenNote 6.1.0

DevPackage mclements/rstpm2

R topics documented:

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AorticStenosisTrials *Aortic Stenosis RCT data*

Description

Data from 5 randomized controlled trials of transcatheter aortic valve replacement vs surgery in patients with Aortic Stenosis. For each RCT and respective primary endpoint, we reconstructed the individual patient data from each randomization group. We first extracted the time and survival probability coordinates from the Kaplan–Meier curves using the DigitizeIt software (<http://www.digitizeit.de/>). We used these coordinates, the total numbers of events, and the numbers of participants at risk to determine individual event times and event indicators.

Usage

```
data(AorticStenosisTrials)
```

Format

An object of class `data.frame` with 5417 rows and 4 columns.

Note

trialID	Name	Minimum of last observed times*
1	NOTION	24.0
2	PARTNER	63.3
3	SURTAVI	24.1
4	PARTNER2	36.1
5	USCoreValve	24.1

* Times for each trial are determined by the minimum of the last observed times across the two randomization groups. All reported times above are in months.

References

- Sondergaard, L, Steinbruchel, DA, Ihlemann, N, Nissen, H, Kjeldsen, BJ, Petersen, P, Ngo, AT, Olsen, NT, Chang, Y, Franzen, OW and others. (2016). Two-year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement. *Circ Cardiovasc Interv* 9(6)
- Mack, MJ, Leon, MB, Smith, CR, Miller, DC, Moses, JW, Tuzcu, EM, Webb, JG, Douglas, PS, Anderson, WN, Blackstone, EH and others. (2015). 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet* 385, 2477-2484.
- Reardon, MJ, Van Mieghem, NM, Popma, JJ, Kleiman, NS, Søndergaard, L, Mumtaz, M, Adams, DH, Deeb, GM, Maini, B, Gada, H and others. (2017). Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 376(14), 1321-1331.
- Leon, MB, Smith, CR, Mack, MJ, Makkar, RR, Svensson, LG, Kodali, SK, Thourani, VH, Tuzcu, EM, Miller, DC, Herrmann, HC and others. (2016). Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 374, 1609-1620.

Deeb, GM, Reardon, MJ, Chetcuti, S, Patel, HJ, Grossman, PM, Yakubov, SJ, Kleiman, NS, Coselli, JS, Gleason, TG, Lee, JS and others. (2016). 3-year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. *J Am Coll Cardiol* 67(22), 2565-2574.

Guyot P, Ades AE, Ouwers MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012; 12:9.

 metaRMSTD

Meta-analysis of RMSTD at multiple time horizons

Description

Perform a meta-analysis with RMSTD using individual patient data. Methods include:

1. "mvma" a multivariate meta-analysis borrowing strength across time-points with within-trial covariance matrix derived analytically
2. "mvma_boot" a multivariate meta-analysis borrowing strength across time-points with within-trial covariance matrix derived by bootstrap
3. "uni" a univariate meta-analysis for combined effect at each time-point using only available data
4. "uni_flex" a univariate meta-analysis for combined effect at each time-point using estimates based on flexible parametric models as described by Wei et al (Stat Med 2015).

Usage

```
metaRMSTD(trialdata, time_horizons, nboot = 500, MA_method)
```

Arguments

trialdata	IPD trial data, see details for specifications
time_horizons	specified vector of time horizons for the meta-analysis
nboot	the number of bootstrap iterations, if using the MVMA with bootstrap covariance matrix; default=500
MA_method	the desired meta-analysis method; options are: "mvma", "mvma_boot", "uni", "uni_flex"

Details

Specify the time horizons at which to calculate the meta-analytic results. The trialdata must be formatted as a dataframe containing the IPD for each single trial including trialID indication. Variable names must include Time ("Time"), Event status ("Event"), and randomization group ("Arm").

Value

The metaRMSTD function returns a list object containing the random effect model results, the RMSTD and SE values for each trial at each available time horizon, and the estimated within-trial covariance matrix for each RCT.

Note

RMSTD is estimable if time horizon > minimum of last observed times. We implement the method of moments estimator for MVMA and Dersimonian and Laird for univariate MA

References

Wei, Y, Royston, P, Tierney, JF and Parmar, MKB. (2015). Meta-analysis of time-to-event outcomes from randomized trials using restricted mean survival time: application to individual participant data. Stat Med 34(21), 2881-2898.

Examples

```
# read in built-in dataset
dat <- AorticStenosisTrials

# meta-analysis to obtain combined effect by multivariate model (method="mvma")
result <- metaRMSTD(dat, time_horizons=c(12,24,36), MA_method="mvma")

# generate figure:
obj <- RMSTcurves(dat, time_horizons=c(12,24,36), tmax=40, nboot=50)
RMSTplot(obj, xlim=c(0,40), ylim=c(-0.25,2.75), yby=0.5, ylab="RMSTD (mos)", xlab="Time (mos)")
```

RMSTcurves	<i>prepare data for plot of RMSTD over time</i>
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Description

Prepare the data for use with [RMSTplot](#). This function computes RMSTD over a specified time interval and also fits a flexible parametric model to each trial. It also computes the estimated combined effects for each of the 4 methods described for [metaRMSTD](#).

Usage

```
RMSTcurves(trialdata, time_horizons, tmax = max(time_horizons),
  tstep = 0.25, nboot = 500, MA_mvma = TRUE, MA_mvma_boot = TRUE,
  MA_uni = TRUE, MA_uni_flex = TRUE)
```

Arguments

trialdata	IPD trial data
time_horizons	specified vector of time horizons for the meta-analysis
tmax	maximum value for RMSTD to be calculated in each trial
tstep	increment for calculation of RMSTD over time interval from 0 to tmax
nboot	the number of bootstrap iterations, if using the MVMA with bootstrap covariance matrix; defaults to nboot=500
MA_mvma	TRUE or FALSE indicates whether to calculate combined effect with this method
MA_mvma_boot	TRUE or FALSE indicates whether to calculate combined effect with this method
MA_uni	TRUE or FALSE indicates whether to calculate combined effect with this method
MA_uni_flex	TRUE or FALSE indicates whether to calculate combined effect with this method

Value

an object to be plotted with [RMSTplot](#)

References

Royston, P. and Parmar, MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat. Med. 2002.

RMSTplot	<i>Plot RMSTD over time interval</i>
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Description

Plot the RMSTcurve object

Usage

```
RMSTplot(RMSTobject, type = "l", col = c("red", "blue", "green",
  "orange", "purple", "yellow", "brown", "gray"), lwd = 2,
  ylim = c(-0.75, 2.75), yby = 0.25, xlim = c(0, 36), xby = 12,
  main = "", xlab = "Time (unit)",
  ylab = "Difference in RMST (unit)", trial_legend = TRUE,
  MA_legend = TRUE, estimates = TRUE)
```

Arguments

RMSTobject	object created by RMSTcurves
type	specify plot type (defaults to line plot)
col	option to specify vector of colors for each study
lwd	option to specify line width
ylim	option to specify limits for y axis
yby	option to specify intervals for y axis
xlim	option to specify limits for x axis
xby	option to specify intervals for x axis
main	option to add title
xlab	option to specify x axis label
ylab	option to specify y axis label
trial_legend	option to include a legend for trial colors
MA_legend	option to include a legend for meta-analysis symbols
estimates	option to include meta-analysis estimates and CIs

Value

a plot of RMSTD over time with option to add combined effect estimates and CIs

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*Topic **datasets**

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