Package 'metaRMST'

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Title Meta-Analysis of RMSTD

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URL https://github.com/iweir/metaRMST

Description R implementation of a multivariate meta-analysis of randomized controlled trials (RCT) with the difference in restricted mean survival times (RMSTD). Use this package with individual patient level data from an RCT 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 combined effect estimates and their confidence intervals.

Depends R (>= 3.4.0), rstpm2

Imports mvmeta, meta, survival, survRM2, graphics

License GPL-2

Encoding UTF-8

LazyData true

RoxygenNote 7.2.3

R topics documented:

`AorticStenosisTrials` *Aortic Stenosis RCT data*

Description

Data from 5 randomized controlled trials of transcatheter aortic valve replacement vs surgery in patients with Aortic Stenosis. The outcome is time until death from any cause. For each RCT, we reconstructed the individual patient data for 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. (Guyot, BMC Med Res Method 2012)

Usage

```
data(AorticStenosisTrials)
```

Format

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

Note

Trial ID	Trial Name	Last observed time (months)*
1	NOTION	24.0
2	PARTNER	63.3
3	SURTAVI	24.1
4	PARTNER2	36.1
5	USCoreValve	24.1

* minimum of the last observed times across the two randomization groups.

References

Sondergaard, L, Steinbruchel, DA, Ihlemann, N, Nissen, H, Kjeldsen, BJ, Peturs-son, 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, Mum-taz, 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 orsurgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016(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, Ouwens 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, MA_method, nboot = 500)
```

Arguments

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

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. Variable names must include Trial ID ("trialID"), Time ("Time"), Event status ("Event"), and randomization group ("Arm").

Value

The `metaRMSTD` function returns a list object containing the random-effects 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 across the two groups. We implement the method-of-moments estimator for MVMA (Chen et al. Biometrics 2012, Jackson et al. Biometrical Journ 2013) 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.

Chen, Han, Alisa K. Manning, and Josée Dupuis. "A method of moments estimator for random effect multivariate meta-analysis." Biometrics 68.4 (2012): 1278-1284.

Jackson, Dan, Ian R. White, and Richard D. Riley. "A matrix-based method of moments for fitting the multivariate random effects model for meta-analysis and meta-regression." Biometrical Journal 55.2 (2013): 231-245.

Examples

```
# read in built-in dataset
data(AorticStenosisTrials)


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

# generate figure:
obj <- RMSTcurves(AorticStenosisTrials, time_horizons=c(12,24,36), tmax=40, nboot=500)
RMSTplot(obj, xlim=c(0,40), ylim=c(-0.25,2.75), yby=0.5, ylab="RMSTD (mos)", xlab="Time (mos)")
```

`RMSTcurves` *prepare data for plot of RMSTD over time*

Description

Prepare the data for use with `RMSTplot`. This function computes RMSTD over specified time horizons and also fits a flexible parametric model to each trial. It calls the `metaRMSTD` function to compute the estimated combined effects for each of the 4 methods.

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; default=0.25
nboot	the number of bootstrap iterations, if using the MVMA with bootstrap covariance matrix; default=500
MA_mvma	TRUE or FALSE indicates whether to include combined effect by this method
MA_mvma_boot	TRUE or FALSE indicates whether to include combined effect by this method
MA_uni	TRUE or FALSE indicates whether to include combined effect by this method
MA_uni_flex	TRUE or FALSE indicates whether to include combined effect by 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 *Plot RMST curves in each trial and combined effects*

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 pointwise 95

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