Package 'SMARTAR'

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Type Package

Title Sequential Multiple Assignment Randomized Trial and Adaptive Randomization

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Description Primary data analysis for sequential multiple assignment randomization trial (SMART) and calibration tools for clinical trial planning purposes. \n
The methods used for this package include: \n
(1) Likelihood-based global test (hypothesis test, power calculation) by in Zhong X., Cheng, B., Qian M., Cheung Y.K. (2019) <doi:10.1016/j.cct.2019.105830>. \n
(2) IPWE-based global test (hypotehsis test, power calculation) by Ogbagaber S.B., Karp J., Wahed A.S. (2016) <doi:10.1002/sim.6747>. \n
(3) G estimates (pairwise comparison, power calculation) by Lavori R., Dawson P.W. (2012) <doi:10.1093/biostatistics/kxr016>. \n
(4) IPW estimates (pairwise comparison, power calculation) by Murphy S.A. (2005) <doi:10.1002/sim.2022>. \n
(5) SAMRT with adaptive randomization by Cheung Y.K. (2015) <doi:10.1111/biom.12258>.

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LazyData true

RoxygenNote 7.1.0

Repository CRAN

Imports graphics, MASS, stats

NeedsCompilation no

Depends R (>= 3.5.0)

VignetteBuilder knitr

License MIT + file LICENSE

Suggests knitr, rmarkdown, testthat

URL https://github.com/tonizhong/SMARTAR/

BugReports https://github.com/tonizhong/SMARTAR/issues/

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R topics documented:

`atsmeans` *Identify adaptive treatment strategy and estimate strategy values*

Description

Return a message that lists all the adaptive treatment strategy embedded in SMART design. It also gives the estiamted strategy values and the variance-covariance matrix of estimated values.

Usage

```
atsmeans(
  data,
  family = c("gaussian", "binomial")[1],
  method = c("Gest", "IPW")[1],
  digits = NULL,
  common = FALSE,
  conf = TRUE,
  alpha = 0.05,
  plot = FALSE,
  title = "Strategy values with confidence interval",
  color = "forestgreen",
  ylab = "Strategy value",
  xlab = NULL,
  xtext = NULL,
  pch = 15,
  cex = 2,
  lwd = 3,
  ylim = NULL,
  mar = NULL,
```

```
  cex.axis = 1,
  line = NULL
)
```

Arguments

data	Input data frame of the sequential randomized trial (SMART) data used for analysis. The data should include the variables of stage-specific treatments (At; t=1,2,3), intermediate evaluation (Ot; t=1,2,3) and final primary outcome (Y), where t represent the number of stages embedded in design. If stage-1 treatment (A1) takes into account the information of baseline evaluation, O1 needed to be include in data, otherwise not.
family	A character string to specify the type of final primary outcome. The default is family="gaussian", which refers to the continuous primary outcome. If family="binomial" then the primary outcome will be treated as binary variable.
method	A character string to specify the method of estimation. If method="Gest" then G-computation method is used. If method="IPW" then Inversed Probability Weighting method is used.
digits	An integer indicating the number of decimal places for sequence-specific mean and variance. Default is digits=NULL.
common	If common=TRUE, the pooled variance across all the treatment sequences are used in estimation. Otherwise use the sequence-specific variance. The default is common=FALSE.
conf	If conf=TRUE, output confidence intervals for estimate strategy values. The default is conf=TRUE.
alpha	Type I error rate control for confidence interval. The default is alpha=0.05.
plot	If plot=TRUE, output the graphs of treatment effects with CIs. The default is plot=TRUE.
title	Characters indicating the title of the graphs. Default is "Strategy values with confidence intervals".
color	Characters indicating the color of the graphs. Default is color="forestgreen".
ylab	Characters to specify the label of the vertical axis of the output figure. Default is "Strategy value".
xlab	characters to specify the label of the horizontal axis of the output figure.
xtext	Specification for the text of the horizontal axis of the graphs.
pch	An integer to specify the shape of points in the graphs. The default is pch=15.
cex	An integer to specify the amount by which plotting symbols should be magnified. The default is cex=2.
lwd	An integer to specify the line width, The lines refer to the width of the confidence interval. The default is lwd=1.
ylim	Integers to specify the maximum and minimum value of y axis.
mar	A numerical vector of the form c(bottom, left, top, right) which gives the number of lines of margin to be specified on the four sides of the plot.

`cex.axis`	The magnification to be used for the horizontal axis annotation relative to the current setting of cex.
`line`	Specifying a value for line overrides the default placement of label of the horizontal axis of the graphs.

Value

An object of "value" is return, which contain the index of all the adaptive treatment strategies, strategy-specific sample sizes and estimated values with standardized errors.

- ATS: Index of adaptive treatment strategy from 1 to G, where G is total number of strategies defined in SMART
- ds: Stage-specific decision makings given certain histories corresponding to each strategy. The number of columns of "ds" is defined by strategy and details are shown in the output.
- N: Number of subjects following a strategy.
- value: Estimated strategy values.
- se: standard errors of estimation
- lower.CI: Lower bound of (1-alpha) level confidence interval for strategy values
- upper.CI: Upper bound of (1-alpha) level confidence interval for strategy values

An object of "vmat" is return, which is variance-covariance matrix of estimated strategy values

References

Lavori P.W. and Dawson R. (2007). Improving the efficiency of estimation in randomization trials of adaptive treatment strategies. *Clinical Trials*, 4: 297-308.

Ko and Wahed A.S. (2015). Design of sequentially randomization trials for testing adaptive treatment strategies. *Statistics in Medicine*, 31, 812-830.

Examples

```
atsmeans(data=codiacs,family="gaussian",method="Gest",
conf=TRUE,common=TRUE,alpha=0.05,plot=TRUE,pch=12,lwd=2)
```

---

codiacs *Example data collected from CODIACS trial*

Description

A Example of SMART data - CODIACS

Usage

```
codiacs
```

Format

A dataset with 108 row and 6 variables:

ID Patient ID

A1 Stage-1 treatment

O2 Intermediate response

A2 Stage-2 treatment

Y Final primary outcome

grou Treatment sequence

`getncp` *get non-centralized parameter*

Description

Return the value of non-centralized parameter for the chi-square distribution given type I, II error and degrees of freedom.

Usage

```
getncp(df, alpha = 0.05, beta = 0.2, d = 1e-04, start = 5)
```

Arguments

`df`	Degrees of freedom of chi-square test
`alpha`	Type I error rate of chi-square test. The default alpha=0.05
`beta`	Type II error rate of chi-square test. The default beta=0.20
`d`	Critical value of distance of the searching procedure. The search of non-centralized parameter value stops at the absolute distance between the actual power and the target power less than the value of d. The default value of d=0.0001
`start`	Initial value of searching the non-centralized parameter.

Value

The value of non-centralized parameter for the chi-square distribution

seqmeans *Summarize sequence-specific descriptive statistics*

Description

Return a message that lists all the treatment sequence embedded in SMART design and summarizes all the sequence-specific descriptive statistics. It also provide design diagram of SMART and graphs of sequence-specific descriptive statistics (boxplot for continuous primary outcome and barchart for binary primary outcome).

Usage

```
seqmeans(
  data,
  family = c("gaussian", "binomial")[1],
  plot = "d",
  digits = NULL,
  color = c("yellow", "forestgreen"),
  pch = c(19, 15),
  title = NULL,
  xlab = NULL,
  ylab = NULL,
  xtext = NULL,
  legend = c("Evaluation", "Treatment"),
  reference = TRUE
)
```

Arguments

data	Input data frame of the sequential randomized trial (SMART) data used for analysis. The data should include the variables of stage-specific treatments (At; t=1,2,3), intermediate evaluation (Ot; t=1,2,3) and final primary outcome (Y), where t represent the number of stages embedded in design. If stage-1 treatment (A1) takes into account the information of baseline evaluation, O1 needed to be include in data, otherwise not.
family	A character string to specify the type of final primary outcome. The default is family="gaussian", which refers to the continuous primary outcome. If family="binomial" then the primary outcome will be treated as binary variable.
plot	A character string to specify the output figure. If plot="d" then output the design diagram of SMART; If plot="s" then output boxplot for continuous primary outcome or bar plot for binary primary outcome by sequence. The default is plot="d".
digits	An integer indicating the number of decimal places for sequence-specific mean and variance. Default is digits=NULL.

color	Characters indicating the color of boxplot for continuous primary outcome and barplot for binomial primary outcome. The first Default is “yellow", the second default is c("yellow","forestgreen").
pch	Two integer indicating the point shape of design diagram of SMART. Default is c(19,15).
title	An character indicating the title of boxplot, barplot for primary outcome or design diagram of SMART. For primary outcome, the default is "Primary outcome by treatment sequence (O1,A1,O2...)", for design diagram, the default is "Design diagram of SMART".
xlab	Characters to specify the label of the horizontal axis of the output figure.
ylab	Characters to specify the label of the vertical axis of the output figure.
xtext	Characters indicating the text of x axis boxplot.
legend	Characters to specify the legend of the design diagram of SMART. Default is legend=c("Evaluation","Treatment").
reference	Logic argument to add a reference line to the graph of descriptive statistics of the primary outcome. The value of the reference line is equal to the average of all sequence-specific means. If TRUE, add a reference line (mean of outcome) to boxplot of the primary outcome, otherwise do not add reference line. The default is reference=FALSE.

Value

an object of information of all the treatment sequences and sequences-specific descriptive statistics defined in a SMART data

- SEQ: Index of treatment sequences.
- O1: Baseline evaluation outcome.
- A1: Action of stage-1 treatment.
- O2: Intermeidate outcome evaluated at the end of stage 1.
- A2: Action of stage-2 treatment.
- O3: Intermeidate outcome evaluated at the end of stage 2.
- A3: Action of stage-3 treatment.
- N: Number of subjects following a certain treatment sequence.
- MEAN: Sequence-specified sample mean.
- VAR: Sequence-specified sample variance.

References

Thall P., Millikan R. and Sung H.G. (2000), “Evaluating multiple treatment courses in clinical trials,” *Statistics in Medicine*, 19, 1011-1028

Lavori P. W. and Dawson R. (2000), “A design for testing clinical strategies: biased adaptive within-subject randomization,” *Journal of the Royal Statistical Society, Series A*, 163, 29-38.

Murphy, S. A. (2005), “An experimental design for the development of adaptive treatment strategies,” *Statistics in Medicine*, 24, 1455-1481.

Examples

```
#get descriptive statistics
seqmeans(data=codiacs,family="gaussian",plot="d",digits=2,pch=c(18,14),
xtext=1:4,xlab="SMARTAR design")
seqmeans(data=codiacs, family="gaussian", plot="s",digits=2,
color="lightblue",
title="Primary outcome",ylab="Primary outcome")
```

SMARTAR *SMARTAR: Sequential Multiple Assignment Randomized Trial and Adaptive Randomization.*

Description

Primary data analysis for sequential multiple assignment randomization trial (SMART) and calibration tools for clinical trial planning purposes. It has several innovative features:

- it supports exploratory data analysis (EDA);
- it is the first R package that can construct and directly output simultaneous confidence intervals for ATS comparisons;
- it provides the results of sample size calculation based on varying published statistical methods in two different fashions, the global test and the pairwise test fashion.

Details

As of right now, SMARTAR exports five major functions:

- seqmeans - design diagram, descriptive statistics, and summarized graphs at sequence level;
- atsmeans - descriptive statistics and summarized graphs at adaptive treatment strategy level;
- smartest - results of global test and pairwise tests; output simultaneous CIs for ATS comparison;
- smartsize - results of sample size calculation;
- getncp - value of non-centralized parameter for the chi-square distribution.

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See Also

Useful links:

- https://CRAN.R-project.org/package=SMARTAR
- https://github.com/tonizhong/SMARTAR/
- Report bugs at: https://github.com/tonizhong/SMARTAR/issues/

`smartest` *Conduct statistical tests using a SMART data*

Description

Return a message that contains the results of statistical tests to compare the values of adaptive treatment strategies defined in a SMART data. The statistical tests include (1) a global test (2) a series of pairwise tests.

Usage

```
smartest(
  data,
  family = c("gaussian", "binomial")[1],
  method = c("Gest", "IPW")[1],
  digits = NULL,
  common = FALSE,
  alpha = 0.05,
  adjust = NULL,
  ntest = NULL
)
```

Arguments

`data`	Input data frame of the SMART data used for analysis, which include the variables of stage-1 treatments (A1), intermediate outcome (O2), stage-2 treatment (A2) and final primary outcome (Y). If stage-1 treatment takes into account baseline information, baseline information (O1) also needs to be included.
`family`	A character string to specify the type of final primary outcome. The default is family="gaussian", which refers to the continuous primary outcome. If family="binomial" then the primary outcome will be treated as binary variable.
`method`	Method used to estimate the value of adaptive treatment strategy. "Gest" for G-computation method and "IPW" for Inversed Probabiliy Weight method. Default is method="Gest".
`digits`	An integer indicating the number of decimal places for sequence-specific mean and variance. Default is digits=NULL.
`common`	If common=TRUE, the pooled variance across all the treatment sequences are used in estimation. Otherwise use the sequence-specific variance. The default is common=FALSE.

alpha	Significant level of confidence interval. The default is alpha=0.05.
adjust	A characteristic string to indicate whether the confidence intervals pairwise distance adjusted for multiple comparison. The default is adjust=NULL, which indicated no adjustment for multiple comparison. If adjust="Bon", the CIs are adjusted for the Bonferroni correction.
ntest	Number of pairwise tests adjusted for Bonferroni correction

Value

An objects of "Strategy" is return, which lists all the adaptive treatment strategy defined in the input data with an index number.

- ATS: Index of the treatment adaptive treatment strategy defined in the input dataset
- ds: the sequence of decision makings that define an adaptive treatment strategy
- N: number of subjects following an adaptive treatment strategy in the intut dataset

An objects of "Global.test" is return, which give the result of the global test.

- size: the total number of subjects in the input dataset
- nATS: the total number of adaptive treatment strategies defined in the input dataset
- df: the degrees of freedom of the global test, which is a chisquare test
- chisq: the chisquare test statistics for the global test
- Pvalue: the P-value of the global test

An object of "Pairwise.test"

- label: The labels of pairwise tests. The details of strategies are shown in $Strategy
- diff: Estimated pairwise distance between treatment and control adaptive treatment strategy
- lower.CI: Lower bound of confidence interval for pairwise distance
- upper.CI: Upper bound of confidence interval for pairwise distance
- Z: Test statistics of pairwise test
- P-value: P-value of pairwise test

References

Murphy, S. A. (2005),"An experimental design for the development of adaptive treatment strategies" *Statistics in Medicine*, 24, 1455-1481.

Ogbagaber S. B., Karp, J., and Wahed A.S. (2015), "Design of sequentially randomization trials for testing adaptive treatment strategies," *Statistics in Medicine*, DOI: 10.1002/sim.6747.

Examples

```
smartest(data=codiacs,family="gaussian",method="Gest",
common=FALSE,alpha=0.05,adjust="Bon")
```

`smartsize` *sample size calculation*

Description

Return a message that contains the estimated strategy-specified means and their confidence interval, as well as the asymptotic variance-covariance matrix for these estimates.

Usage

```
smartsize(
  sim = NULL,
  delta = NULL,
  df = NULL,
  alpha = 0.05,
  beta = 0.2,
  global = TRUE,
  family = c("gaussian", "binomial")[1]
)
```

Arguments

`sim`	A numeric matrix containing the values of treatment sequence-specific parameters to generate the SMART data, including the values of stage-specific treatments, intermediate outcome and final primary outcome.
`delta`	The standardized effect size for sample size calculation.
`df`	The degrees of freedom for the chisquare test.
`alpha`	Type I error rate.
`beta`	Type II error rate.
`global`	If TRUE then power the SMART based on a global test, otherwise power the SMART based on a pairwise test. The default is TRUE
`family`	A character string to specify the type of final primary outcome. The default is family="gaussian", which refers to the continuous primary outcome. If family="binomial" then the primary outcome will be treated as binary variable.

Value

Standardized effect size and total sample size for SMART

- delta: standardized effect size
- n: total sample size

References

Murphy, S. A. (2005). An experimental design for the development of adaptive treatment strategies. Statistics in Medicine. 24(10): 1455-1481.

Ogbagaber S. B., Karp, J., and Wahed A.S. (2015). Design of sequentially randomization trials for testing adaptive treatment strategies. Statistics in Medicine. DOI: 10.1002/sim.6747.

`summary.myclass` *Summarize the dataframe got from the package*

Description

Summarize the result of sequential primary outcome in ‘seqmeans‘ and the estimated strategy values in ‘atsmeans‘

Usage

```
## S3 method for class 'myclass'
summary(object, ...)
```

Arguments

`object`	A dataframe to be summarized
`...`	other arguments in summary generic function

Value

Descriptive table of the dataframe is returned

Examples

```
ats_outcome=atsmeans(data=codiacs,conf=TRUE,
 alpha=0.05,digits = 2,pch=18,xlab="abc")
summary(ats_outcome)
```

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