Package 'SAME'

January 20, 2025

Type Package

Title Seamless Adaptive Multi-Arm Multi-Stage Enrichment

Version 0.1.0

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Description Design a Bayesian seamless multi-arm biomarker-enriched phase II/III design with the survival endpoint with allowing sample size re-estimation.
James M S Wason, Jean E Abraham, Richard D Baird, Ioannis Gournaris, Anne-Laure Vallier, James D Brenton, Helena M Earl, Adrian P Mander (2015) <doi:10.1038/bjc.2015.278>.
Guosheng Yin, Nan Chen, J. Jack Lee (2018) <doi:10.1007/s12561-017-9199-7>.
Ying Yuan, Beibei Guo, Mark Munsell, Karen Lu, Amir Jazaeri (2016) <doi:10.1002/sim.6971>.

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Encoding UTF-8

LazyData true

RoxygenNote 7.2.1

Imports boot, rjags, coda, extraDistr, survival, ggplot2, expint

Suggests testthat, mockery, knitr, rmarkdown

Depends R (>= 3.3.0)

NeedsCompilation no

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Repository CRAN

Date/Publication 2023-01-16 10:10:08 UTC

Contents

`conduct.phase2` *Function to identify the most promising treatment-biomarker-linked subgroup*

Description

This function is used to estimate the effect size of each subgroup and to select the most promising subgroup.

Usage

```
conduct.phase2(formula, surv, event, data)
```

Arguments

`formula`	a formula object, with the combinations of treatment and biomarker term, e.g., formula = "T1:B1+T1:B2+T2:B1+T2:B2"
`surv`	survival time
`event`	the status indicator, 0=alive, 1=dead
`data`	a data.frame in which to interpret the variables named in the formula

Value

conduct.phase2() select the most effective subgroup and returns the estimated hazard ratio.

Examples

```
conduct.phase2(formula = "T1:B1+T1:B2+T2:B1+T2:B2", surv = "surv",
event = "death", data = "example.1")
```

`conduct.phase3` *Function to estimate the hazard ratios and other statistics of the selected subgroup*

Description

This function is used to estimate the effect size of the selected subgroup.

Usage

```
conduct.phase3(data, eta, theta)
```

Arguments

`data`	a data.frame in which to interpret the variables named in the formula
`eta`	a cutoff probability for the strength of evidence for decision-making
`theta`	a clinically meaningful treatment effect size defined by clinicians

Value

conduct.phase3()

Examples

```
conduct.phase3(example.2,eta=0.8, theta=0.95)
```

`example.1` *A Time-to-event dataset containing the time and other attributes of 643 patients.*

Description

A Time-to-event dataset containing the time and other attributes of 643 patients.

Usage

```
example.1
```

Format

A data frame with 643 rows and 6 variables:

T1 binary variable, receive treatment 1=1, not receive treatment 1=0

T2 binary variable, receive treatment 2=1, not receive treatment 2=0

B1 binary variable, biomarker 1 positive=1, biomarker 1 negative=0

B2 binary variable, biomarker 2 positive=1, biomarker 2 negative=0

death the status indicator, alive=0, dead=1

surv survival time or follow up time ...

`example.2` *A Time-to-event dataset containing the time and other attributes of 643 patients.*

Description

A Time-to-event dataset containing the time and other attributes of 643 patients.

Usage

```
example.2
```

Format

A data frame with 643 rows and 6 variables:

T1 binary variable, receive treatment 1=1, not receive treatment 1=0

T2 binary variable, receive treatment 2=1, not receive treatment 2=0

B1 binary variable, biomarker 1 positive=1, biomarker 1 negative=0

B2 binary variable, biomarker 2 positive=1, biomarker 2 negative=0

death the status indicator, alive=0, dead=1

surv survival time or follow up time

survtime survival time or follow up time

treatments categorical vairable, indicating treatments received ...

`find.cutoffs` *Function to calibrate the cutoff points under null hypothesis*

Description

This function is used to calibrate the cutoff points under null hypothesis using a multi-arm multi-stage biomarker-enriched design with time-to-event endpoints.

Usage

```
find.cutoffs(
  median.c,
  K,
  L,
  lfu,
  alpha,
  power,
  accrate,
  theta,
  bio.preva,
  FAtime.phase3,
  N.iter
)
```

Arguments

`median.c`	The median survival time for control group
`K`	Number of biomarkers
`L`	Information fraction in terms of the accumulative events in phase II stage, e.g., K = c(1/4,1/2,1)
`lfu`	Follow-up time
`alpha`	One-sided familywise error rate
`power`	Power
`accrate`	Accrual rate
`theta`	A clinically meaningful treatment effect size defined by clinicians
`bio.preva`	Prevalence of biomarker(s)
`FAtime.phase3`	the study ending time of phase III
`N.iter`	Number of iterations

Value

find.cutoffs() returns the calibrated cutoff points that can control the type I error rate.

Examples

```
find.cutoffs(median.c=12,K=2,L=c(1/4,1/2,1),lfu=0,alpha=0.05,power=0.9,
             accrate=15,theta=log(1.25),bio.preva=c(0.4,0.6),FAtime.phase3=48,
             N.iter=3)
```

`sim.trial` *Function to simulate Bayesian seamless multi-arm biomarker-enriched phase II/III designs*

Description

This function finds the required number of events
using a multi-arm multi-stage biomarker-enriched design with time-to-event endpoints.

Usage

```
sim.trial(
  median.c,
  hr,
  K,
  L,
  lfu,
  alpha,
  power,
  accrate,
  theta,
  bio.preva,
  FAtime.phase3,
  N.iter
)
```

Arguments

`median.c`	The median survival time for control group
`hr`	Alternative hazard ratio
`K`	Number of biomarkers
`L`	Information fraction in terms of the accumulative events in phase II stage, e.g., K = c(1/4,1/2,1)
`lfu`	Follow-up time
`alpha`	One-sided familywise error rate
`power`	Power
`accrate`	Accrual rate
`theta`	A clinically meaningful treatment effect size defined by clinicians

bio.preva	Prevalence of biomarker(s)
FAtime.phase3	the study ending time of phase III
N.iter	Number of iterations

Value

sim_trial() returns the nominal type I error rate and calibrated cutoff points, nominal power under user-defined hypothesis, empirical power under user-defined number of simulations, the duration of trial(time), the number of events (num_evs), the number of patients (num_pts) from different stages. The function can also display the number of events and patients under the selected subgroup, the distribution of decision zones and the estimated hazard ratio for the final analysis.

Examples

```
sim.trial(median.c=12,hr=c(1,1,1,0.6),K=2,L=c(1/4,1/2,1),lfu=0,
          alpha=0.05,power=0.9,accrate=15,theta=log(1.25),
          bio.preva=c(0.4,0.6),FAtime.phase3=48,N.iter=5)
```

---

sim.trial.2 *Function to simulate Bayesian seamless multi-arm biomarker-enriched phase II/III designs with user-defined cutoff points*

Description

This function finds the required number of events using a multi-arm multi-stage biomarker-enriched design with time-to-event endpoints with the user-defined cutoff points.

Usage

```
sim.trial.2(
  median.c,
  hr,
  K,
  L,
  lfu,
  alpha,
  power,
  accrate,
  theta,
  bio.preva,
  FAtime.phase3,
  eta,
  futility,
  superiority,
  N.iter
)
```

Arguments

median.c	The median survival time for control group
hr	Alternative hazard ratio
K	Number of biomarkers
L	Information fraction in terms of the accumulative events in phase II stage, e.g., K = c(1/4,1/2,1)
lfu	Follow-up time
alpha	One-sided family-wise error rate
power	Power
accrate	Accrual rate
theta	A clinically meaningful treatment effect size defined by clinicians
bio.preva	Prevalence of biomarker(s)
FAtime.phase3	the study ending time of phase III
eta	A cutoff probability for the strength of evidence for decision-making and defined by user.
futility	cutoff point for futility termination
superiority	cutoff point for superiority termination
N.iter	Number of iterations

Value

sim.trial.2() returns the nominal type I error rate, nominal power under user-defined hypothesis, empirical power under user-defined number of simulations, the duration of trial(time), the number of events (num_evs), the number of patients (num_pts) from different stages. The function can also display the number of events and patients under the selected subgroup, the distribution of decision zones and the estimated hazard ratio for the final analysis.

Examples

```
sim.trial.2(median.c=12,hr=c(1,1,1,0.6),K=2,L=c(1/4,1/2,1),lfu=0,alpha=0.05,
            power=0.9,accrate=15,theta=log(1.25),bio.preva=c(0.4,0.6),
            FAtime.phase3=48,eta=0.2,futility=0.1,superiority=0.9,
            N.iter=3)
```

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