Package 'monitOS'

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Title Monitoring Overall Survival in Pivotal Trials in Indolent Cancers

URL https://opensource.nibr.com/monitOS/, https://github.com/Novartis/monitOS

BugReports https://github.com/Novartis/monitOS/issues

Version 0.1.6

Description These guidelines are meant to provide a pragmatic, yet rigorous, help to drug developers and decision makers, since they are shaped by three fundamental ingredients: the clinically determined margin of detriment on OS that is unacceptably high (delta null); the benefit on OS that is plausible given the mechanism of action of the novel intervention (delta alt); and the quantity of information (i.e. survival events) it is feasible to accrue given the clinical and drug development setting. The proposed guidelines facilitate transparent discussions between stakeholders focusing on the risks of erroneous decisions and what might be an acceptable trade-off between power and the false positive error rate.

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Contents

`app_server` *Shiny app server*

Description

Shiny app server

Usage

```
app_server(input, output, session)
```

Arguments

`input`	generic shiny var
`output`	generic shiny var
`session`	generic shiny var

app_ui *Shiny app UI*

Description

Shiny app UI

Usage

```
app_ui(request)
```

Arguments

request	generic shiny var

bounds *Bounds*

Description

OS monitoring guidelines as proposed in manuscript "Monitoring Overall Survival in Pivotal Trials in Indolent Cancers". Calculate thresholds for positivity that can be used at an analysis to judge whether emerging evidence about the effect of treatment on OS is concerning or not. The threshold for positivity at any given analysis is the value below which the observed hazard ratio must be in order to provide sufficient reassurance that the effect on OS does not reach the selected unacceptable level of detriment (the margin hr_null). Terminology follows the manuscript "Monitoring Overall Survival in Pivotal Trials in Indolent Cancers"

Usage

```
bounds(
  events,
  power_int = 0.9,
  falsepos = 0.025,
  hr_null = 1.3,
  hr_alt = 0.9,
  rand_ratio = 1,
  hr_marg_benefit = NULL
)
```

Arguments

events	Vector. Target number of deaths at each analysis
power_int	Scalar. Marginal power required at the Primary Analysis when true hazard ratio (HR) is hr_alt.
falsepos	Scalar. Marginal one-sided false positive error rate we are prepared to tolerate at the Final Analysis. Determines the positivity threshold at Final Analysis
hr_null	Scalar. The unacceptably large detrimental effect of treatment on OS we want to rule out (on HR scale)
hr_alt	Scalar. Plausible clinically relevant beneficial effect of treatment on OS (on HR scale)
rand_ratio	Integer. If patients are randomized k:1 between experimental intervention and control, rand_ratio should be inputted as k. Example: if patients are randomized 1:1 between experimental and control, k=1. If patients are randomized 2:1 between experimental and control, k=2.
hr_marg_benefit	Scalar. We may be uncertain about what a plausible beneficial effect of treatment on OS is. User can enter a (on HR scale) and function will evaluate the probability we meet the positivity threshold at each analysis under this HR. This second OS benefit will usually be closer to 1 than hr_alt.

Details

Monitoring guidelines assume that the hazard ratio (HR) can adequately summarize the size of the benefits and harms of the experimental intervention vs control on overall survival (OS). Furthermore, guidelines assume that an OS HR < 1 is consistent with a beneficial effect of the intervention on OS (and smaller OS HRs <1 indicate increased efficacy).

Value

List that contains:

- `lhr_null`: Scalar, unacceptable OS log-HR,
- `lhr_alt`: Scalar, plausible clinically relevant log-HR,
- `lhr_pos`: Scalar, positivity thresholds for log-HR estimates,
- `summary`: Dataframe, which contains:
  - `OS HR threshold for positivity`,
  - `One sided false positive error rate`,
  - `Level of 2 sided CI needed to rule out hr_null`,
  - `Probability of meeting positivity threshold under hr_alt`,
  - `Positivity_Thres_Posterior`: Pr(true OS HR >= minimum unacceptable OS HR | current data),
  - `Positivity_Thres_PredProb`: Pr(OS HR estimate at Final Analysis <= Final Analysis positivity threshold | current data)

Examples

```
# Example 01: OS monitoring guideline retrospectively applied to Motivating Example 1
# with delta null = 1.3, delta alt = 0.80, gamma_FA = 0.025 and  beta_PA = 0.10.
bounds(
  events = c(60, 89, 110, 131, 178),
  power_int = 0.9, # beta_PA
  falsepos = 0.025, # gamma_FA
  hr_null = 1.3, # delta_null
  hr_alt = 0.8, # delta_alt
  rand_ratio = 1, # rand_ratio
  hr_marg_benefit = NULL
)
# Example 02: OS monitoring guideline applied to Motivating Example 2
# with delta null = 4/3, delta alt = 0.7, gamma_FA = 0.20 and beta_PA = 0.1.
bounds(
  events = c(60, 89, 110, 131, 178),
  power_int = 0.9, # beta_PA
  falsepos = 0.025, # gamma_FA
  hr_null = 1.3, # delta_null
  hr_alt = 0.8, # delta_alt
  rand_ratio = 1, # rand_ratio
  hr_marg_benefit = 0.95
)
```

---

calc_posterior *Function which calculates for k=1, ..., K, Pr(log-HR >= lhr_null | theta.hat.k = lhr_con.k)*

Description

i.e. the posterior probability the true OS log-hr exceeds the minimum unacceptable OS log-HR given the estimate of the log-hr at analysis k equals lhr_con.k (i.e. the estimate is equal to the stage k 'continuation threshold').

Usage

```
calc_posterior(lhr_con, lhr_null, events)
```

Arguments

lhr_con	vector of length K (# number of looks at OS data) containing 'continuation' thresholds on log-HR scale
lhr_null	scalar - minimum unacceptable OS log-HR
events	vector length K - number of OS events at each look at the data

Value

vector of length K - continuation thresholds expressed on posterior probability scale

Examples

```
lhr_con <- c(0.2, 0.15, 0.1)
lhr_null <- 0.25
events <- c(100, 200, 300)
calc_posterior(lhr_con, lhr_null, events)
```

`calc_predictive` *Calculate posterior predictive probability of ruling out lhr_null at final OS analysis*

Description

Calculates the posterior predictive probability of 'ruling out' lhr_null at final OS analysis given current estimate of OS log-HR is lhr_cont_k, for k=1, ..., K-1

Usage

```
calc_predictive(lhr_con, events)
```

Arguments

`lhr_con`	vector of length K (# number of looks at OS data) containing 'continuation' thresholds on log-HR scale
`events`	vector length K - number of OS events at each look at the data

Value

vector of length K-1: continuation thresholds at analyses k=1, ..., K-1 expressed on scale of posterior predictive probability of ruling out lhr_null at final OS analysis

Examples

```
lhr_con <- c(0.2, 0.15, 0.1)
events <- c(100, 200, 300)
calc_predictive(lhr_con, events)
```

find_pos *Find Positivity Threshold*

Description

This function calculates the positivity threshold based on various criteria.

Usage

```
find_pos(pos_thld, events, rand_ratio, hr_null, hr_alt, which_crit, targ)
```

Arguments

pos_thld	Numeric. The initial positivity threshold.
events	Numeric vector of length 2. The number of events at each analysis.
rand_ratio	Numeric. The randomization ratio.
hr_null	Numeric. The hazard ratio under the null hypothesis.
hr_alt	Numeric. The hazard ratio under the alternative hypothesis.
which_crit	Integer. The criterion to be used for finding the positivity threshold: • 1: False positive / False negative equals required value. • 2: False positive / (False negative + False positive) equals required value. • 3: False positive equals required value. • 4: Predictive probability equals required value.
targ	Numeric. The target value for the chosen criterion.

Value

Numeric. The calculated positivity threshold based on the specified criterion.

Examples

```
find_pos(
  pos_thld = 1.5,
  events = c(100, 200),
  rand_ratio = 1,
  hr_null = 1,
  hr_alt = 1.5,
  which_crit = 1,
  targ = 0.05
)
```

meeting_probs *Probabilities of meeting positivity threshold under target HR*

Description

Probabilities of meeting positivity threshold under target HR

Usage

```
meeting_probs(summary, lhr_pos, lhr_target = 1, rand_ratio = 1)
```

Arguments

summary	DataFrame. Summary dataframe from bounds.R
lhr_pos	List. Log HRs for positive threshold
lhr_target	Scalar. Target log HR to calculate the probability of meeting positivity thresholds
rand_ratio	Integer. If patients are randomized k:1 between experimental intervention and control, rand_ratio should be inputted as k. Example: if patients are randomized 1:1 between experimental and control, k=1. If patients are randomized 2:1 between experimental and control, k=2.

Value

Array. Probabilities of meeting positivity threshold under target HR

run_app *monitOS app*

Description

Runs the shiny app to guide user choice adequate settings to calculate the positivity thresholds to monitor overall survival (OS)

Usage

```
run_app()
```

Value

No return value, runs shiny app

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