Package 'FutilityStopping'

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Type Package

Title Futility Evaluation on the Clinical Endpoint using Early Read Outs

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Author Kelly Van Lancker

Maintainer Kelly Van Lancker <kelly.vanlancker@ugent.be>

Description
Includes a number of functions that are useful for futility evaluations and simulations of (simulated) clinical trials with interim analyses incorporating short- and long-term endpoints.

License GPL (>=2)

Imports ggplot2, stats, graphics

NeedsCompilation no

R topics documented:

`determine.Cutoff` *Determining the cut-off value for the expected conditional power.*

Description

The cut-off value for the expected conditional power is determined based on a maximum reduction in power under one or more chosen scenarios.

Usage

```
determine.Cutoff(n.1, n.0, n.coh1.1, n.coh1.0, n.interim.1, n.interim.0,
                           prior.1 = c(0, 0, 0, 0), prior.0 = c(0, 0, 0, 0),
                           p.pe.1_cp = NULL, p.pe.0_cp = NULL,
                           alternative = c("greater"), alpha = 0.025,
                           method = c("analytical"), assumption = c("design"),
                           n.simqk = 2500, n.trials = 10000, ni.margin = 0,
                           p.er.1, p.er.0, p.pe.1, p.pe.0,
                           log.OR.1, log.OR.0, max.PowerReduction)
```

Arguments

`n.1, n.0` Total number of subjects planned in the experimental/control arm.

`n.coh1.1, n.coh1.0`
Total number of subjects planned in cohort 1 of the experimental/control arm.

`n.interim.1, n.interim.0`
Planned number of subjects with early response data available at the time of the interim analysis in the experimental/control arm.

`prior.1, prior.0`
Summary vector of hypothetical or historical X and Y data in the experimental/control arm:

- early responders ($X = 1$) for whom $Y = 1$,
- early responders ($X = 1$) for whom $Y = 0$,
- early non-responders ($X = 0$) for whom $Y = 1$, and
- early non-responders ($X = 0$) for whom $Y = 0$.

Default c(0, 0, 0, 0), corresponding to non-informative priors based on a 2x2 table with 0.5 in each cell.

`p.pe.1_cp, p.pe.0_cp`
Assumed design rate to achieve a favorable primary outcome ($Y = 1$) in the experimental/control arm.

`alternative` A character string specifying the alternative hypothesis, must be `"greater"` (default) or `"less"`.

`alpha` One-sided significance level at which the primary hypothesis will be tested. Default 0.025.

`method` A character string specifying the method, must be one of `"simulation"` (default) or `"analytical"`. The `"simulation"`-method calculates the conditional power via simulations, while the `"analytical"`-method approximates the conditional power via analytical expressions following Lan and Wittes using a test statistic with a normal approximation (this would reduce the computational intensity).

`assumption` A character string specifying the assumption under which the (expected) conditional power is calculated, must be one of `"design"` (default) or `"trend"`.

`n.simqk` The number of nuisance parameter sets $(P^d_{Y_1|X_1=1}, P^d_{Y_1|X_1=0}, P^d_{Y_0|X_0=1}, P^d_{Y_0|X_0=0})$ sampled from the posterior density (Van Lancker et al., 2019). Default 2000.

`n.trials` Number of simulated trials (interim datasets). Default 10000.

`ni.margin` Default value of 0 is set to test for superiority; negative values are used for non-inferiority.

`p.er.1, p.er.0` Vector of proportions of subjects achieving a favorable early response in the experimental/control arm.

`p.pe.1, p.pe.0` Vector of proportions of subjects achieving a favorable primary outcome in the experimental/control arm.

`log.OR.1, log.OR.0`
Vector of log odds ratios between the presence/absence of X (early endpoint) and the presence/absence of Y (primary endpoint) in the experimental/control arm for the different prespecified scenarios.

`max.PowerReduction`
Vector of maximal allowed power reductions for the different prespecified scenarios.

Value

An object of class `determine.Cutoff` with components,

`cutoff` Cutoff determined based on the maximum power reduction for the prespecified scenarios.

`simulation.results`
Results of the simulation studies for the prespecified scenarios used to determine the cutoff.

See Also

`Ecp`, `sim.Ecp`

Examples

```
# Let us assume a superiority scenario whereby the proportion of subjects achieving the early
# response is the same as the proportion of subjects achieving the primary outcome.
# The data generating models for efficacy data are then given by:
#
# Group     P(X=1)     P(Y=1)     log(OR)
# Exp.       0.73       0.73        7.4
# Contr.     0.60       0.60        4.1
#
#
# In each of the 5000 simulated trials, 550 subjects are enrolled and interim data were available
# for 220 of these subjects, 120 of them had info on both the early and primary endpoint.
# Data from a previous study
#
# Group      (X=1, Y=1)       (X=1, Y=0)        (X=0, Y=1)        (X=0, Y=0)
# Exp.           43               9                 1                 13
# Contr.         26               12                5                 23
#
# Furthermore, the assumed (design) rates of achieving the primary endpoint are 0.73
# in the experimental group and 0.60 in the control group.

# Determination of cutoff:
fit <- determine.Cutoff(n.1=275, n.0=275, n.coh1.1=60, n.coh1.0=60,
                        n.interim.1=110, n.interim.0=110,
                        prior.1 = c(43, 9, 1, 13), prior.0 = c(26, 12, 5, 23),
                        p.pe.1_cp = 0.73, p.pe.0_cp = 0.60,
                        alternative = c("greater"), alpha = 0.025,
                        method = c("analytical"), assumption = c("design"),
```

```
   n.simqk = 200, n.trials = 50, ni.margin = 0,
p.er.1=c(0.73), p.er.0=c(0.60), p.pe.1=c(0.73), p.pe.0=c(0.60),
   log.OR.1=c(7.4), log.OR.0=c(4.1), max.PowerReduction = 0.01)
```

Ecp *Calculates the expected conditional power of a clinical trial based on the data available at the point of an interim analysis.*

Description

This function returns the expected conditional power, defined as the probability to reject the null hypothesis (e.g., of no difference in the proportion of subjects achieving the primary endpoint Y between the experimental and control group) at the end of the trial conditionally on the observed data at interim. The endpoints for evaluation at the interim analysis are the early response (X) and primary endpoint response (Y). Based on this, the following three cohorts of subjects can be distinguished:

In a first cohort, the primary endpoint (Y) has been observed. In a second cohort, X has already been observed but the long term Y not. Under the assumption that X is a predictor for the primary endpoint Y, the observed X values contain information on the unobserved Y values. To that end, the observed Y data from cohort 1 is augmented with the observed X data (cohorts 1 and 2) when evaluating conditional power. A third cohort contains subjects for whom no data are available yet. For this cohort, the design assumed rates of achieving the primary endpoint in the experimental and control group are used.

Prediction of Y data from X data observed in cohort 2 can be accomplished using a repeated binary data model on the data pairs (X, Y) by estimating the conditional probabilities to achieve Y for early responders $P(Y|X = 1)$ and early non-responders $P(Y|X = 0)$. The conditional power is a function of the observed Y (cohort 1), predicted Y (cohort 2) and the effect size in cohort 3 (design assumed Y).

Both superiority and non-inferiority trials are considered. For a detailed analytical description of the methodology see Van Lancker et al., 2019.

Usage

```
Ecp(n.1, n.0, coh1.er.pe.1, coh1.er.pe.0, coh2.er,
    prior.1 = c(0, 0, 0, 0), prior.0 = c(0, 0, 0, 0),
   p.pe.1_cp = NULL, p.pe.0_cp = NULL, alternative = c("greater"), alpha = 0.025,
    method = c("simulation"), assumption = c("design"),
    n.simqk = 2500, ni.margin = 0
    )
```

Arguments

`n.1, n.0` Total number of subjects planned in the experimental/control arm.

`coh1.er.pe.1, coh1.er.pe.0`
Vectors containing the number of subjects in cohort 1 of the experimental/control arm:

- early responders ($X = 1$) for whom $Y = 1$,
- early responders ($X = 1$) for whom $Y = 0$,

- early non-responders ($X = 0$) for whom $Y = 1$, and
- early non-responders ($X = 0$) for whom $Y = 0$.

`coh2.er` A vector containting the number of

- early responders ($X = 1$) in the experimental arm,
- early responders ($X = 1$) in the control arm,
- early non-responders ($X = 0$) in the experimental arm, and
- early non-responders ($X = 0$) in the control arm

of cohort 2.

`prior.1, prior.0`
Summary vector of hypothetical or historical X and Y data in the experimental/control arm:

- early responders ($X = 1$) for whom $Y = 1$,
- early responders ($X = 1$) for whom $Y = 0$,
- early non-responders ($X = 0$) for whom $Y = 1$, and
- early non-responders ($X = 0$) for whom $Y = 0$.

Default c(0, 0, 0, 0), corresponding to non-informative priors based on a 2x2 table with 0.5 in each cell.

`p.pe.1_cp, p.pe.0_cp`
Assumed design rate to achieve a favorable primary outcome ($Y = 1$) in the experimental/control arm.

`alternative` A character string specifying the alternative hypothesis, must be `"greater"` (default) or `"less"`.

`alpha` One-sided significance level at which the primary hypothesis will be tested. Default 0.025.

`method` A character string specifying the method, must be one of `"simulation"` (default) or `"analytical"`. The `"simulation"`-method calculates the conditional power via simulations, where the `"analytical"`-method approximates the conditional power via analytical expressions following Lan and Wittes using a test statistic with a normal approximation (this would reduce the computational intensity). See details.

`assumption` A character string specifying the assumption under which the (expected) conditional power is calculated, must be one of `"design"` (default) or `"trend"`.

`n.simqk` The number of nuisance parameter sets $(P^d_{Y_1|X_1=1}, P^d_{Y_1|X_1=0}, P^d_{Y_0|X_0=1}, P^d_{Y_0|X_0=0})$ sampled from the posterior density (Van Lancker, 2018). Default 2000.

`ni.margin` Default value of 0 is set to test for superiority; negative values are used for non-inferiority.

Details

The analytical method is based on the assumption that the ratio of the number of subjects in the experimental arm to the number of subjects in the control arm is equal to the ratio of the number of subjects in the experimental arm of cohort 1 to the number of subjects in the control arm of cohort 1, equal to the ratio of the number of subjects in the experimental arm of cohort 1 to the number of subjects in the control arm of cohort 2 and equal to the ratio of the number of subjects in the experimental arm of cohort 1 to the number of subjects in the control arm of cohort 3. Note that in practice, if these equalities do not apply, then the ratios are at least approximately equal by randomization.

Value

An object of class `Ecp` with components,

`ExpectedConditionalPower`
: The expected conditional power based on the data collected up to the point of the interim analysis.

`eta`
: The sampled nuisance parameter sets $(P^d_{Y_1|X_1=1}, P^d_{Y_1|X_1=0}, P^d_{Y_0|X_0=1}, P^d_{Y_0|X_0=0})$.

`cp_values`
: The calculated conditional power values corresponding to each nuisance parameter set $(P^d_{Y_1|X_1=1}, P^d_{Y_1|X_1=0}, P^d_{Y_0|X_0=1}, P^d_{Y_0|X_0=0})$.

`n.1, n.0`
: Total number of subjects planned in the experimental/control arm.

`coh1.er.pe.1, coh1.er.pe.0`
: Vectors containing the number of subjects in cohort 1 of the experimental/control arm:
  - early responders ($X = 1$) for whom $Y = 1$,
  - early responders ($X = 1$) for whom $Y = 0$,
  - early non-responders ($X = 0$) for whom $Y = 1$, and
  - early non-responders ($X = 0$) for whom $Y = 0$.

`coh2.er`
: A vector containting the number of
  - early responders ($X = 1$) in the experimental arm,
  - early responders ($X = 1$) in the control arm,
  - early non-responders ($X = 0$) in the experimental arm, and
  - early non-responders ($X = 0$) in the control arm

  of cohort 2.

`p.pe.1_cp, p.pe.0_cp`
: Assumed design rate to achieve a favorable primary outcome ($Y = 1$) in the experimental/control arm.

Note

Be careful with the order of the vector elements.

Examples

```
# A study comparing a new treatment versus placebo planned to enroll 550 subjects
# to test the null hypothesis of no difference in the proportion of cured subjects
# after 1 year. Interim data (after 6 months) was available for 220 of these subjects,
# 120 of them had info on both the early and primary endpoint.
#
# Data in cohort 1:
#
# Group      (X=1, Y=1)       (X=1, Y=0)        (X=0, Y=1)        (X=0, Y=0)
# Exp.           43               1                 0                16
# Contr.         37               1                 0                22
#
# Data in cohort 2:
#
# Group       X=1    X=0
# Exp.        37     13
# Contr.      36     14
#
```

```
# Data from a previous study:
#
# Group      (X=1, Y=1)      (X=1, Y=0)        (X=0, Y=1)        (X=0, Y=0)
# Exp.           43               9                 1                 13
# Contr.         26               12                5                 23
#
# Furthermore, the assumed rates of achieving the primary endpoint are 0.73 in the experimental
# group and 0.60 in the control group.


# Calculate the expected conditional power
fit <- Ecp(n.1 = 275, n.0 = 275, coh1.er.pe.1 = c(43, 1, 0, 16),
           coh1.er.pe.0 = c(37, 1, 0, 22), coh2.er = c(37, 36, 13, 14),
           prior.1 = c(43, 9, 1, 13), prior.0 = c(26, 12, 5, 23),
           p.pe.1_cp = 0.73, p.pe.0_cp = 0.60, alternative = c("greater"),
           alpha = 0.025, method = c("analytical"), n.simqk = 100,
           ni.margin = 0)


# Examine results
summary(fit)
```

`plot.Ecp` *Plot Diagnostics for an Ecp Object*

Description

Two plots representing the influence of the $(P(Y|X=1), P(Y|X=0))$-pairs on the conditional power values in both treatment groups, selectable by treatment.

Usage

```
## S3 method for class 'Ecp'
plot(x, group = "treatment",
                    Par = par(oma = c(0, 0, 0, 0), mar = c(5.1, 4.1, 4.1, 2.1)),
                      ...)
```

Arguments

`x`	An object of the class `Ecp`
`group`	Specify for which group a plot is required: `group= "treatment"`(default) or `group= "control"`.
`Par`	Graphical parameters for the plot. Default `par(oma = c(0, 0, 0, 0), mar = c(5.1, 4.1, 4.1, 2.`
`...`	Other arguments to be passed.

See Also

Ecp

Examples

```
# Example see Ecp
fit <- Ecp(n.1 = 275, n.0 = 275, coh1.er.pe.1 = c(43, 1, 0, 16),
           coh1.er.pe.0 = c(37, 1, 0, 22), coh2.er = c(37, 36, 13, 14),
           prior.1 = c(43, 9, 1, 13), prior.0 = c(26, 12, 5, 23),
           p.pe.1_cp = 0.73, p.pe.0_cp = 0.60, alternative = c("greater"),
           alpha = 0.025, method = c("analytical"), n.simqk = 100,
           ni.margin = 0)


# Plot the results
plot(fit)
```

`plot.sim.Ecp` *Plotting the probability to stop for futility for different cutoff values.*

Description

This function provides a plot that displays the probability to stop for futility for a serie of conditional power cutoff values and the chosen cutoff. These figures are useful to determine a decision rule for stopping the trial with reasonable performance.

Usage

```
## S3 method for class 'sim.Ecp'
plot(x, xlab, ylab, main,
                    Par = par(oma = c(0, 0, 0, 0), mar = c(5.1, 4.1, 4.1, 2.1)),
                      ...)
```

Arguments

`x`	An object of the class `sim.Ecp`
`xlab`	A title for the x-axis. Default `xlab = "Conditional Power Cutoff"`.
`ylab`	A title for the y-axis. Default `ylab = "P(Stop for Futility)"`.
`main`	An overall title for the plot. Default `main = "Simulation Results"`.
`Par`	Graphical parameters for the plot. Default `par(oma = c(0, 0, 0, 0), mar = c(5.1, 4.1, 4.1, 2.`
`...`	Other arguments to be passed.

See Also

sim.Ecp

Examples

```
# Example see \link{sim.Ecp}
fit <- sim.Ecp(n.1= 275, n.0= 275, n.coh1.1 = 60, n.coh1.0 = 60,
               n.interim.1 = 110, n.interim.0 = 110,
               prior.1 = c(43, 9, 1, 13), prior.0 = c(26, 12, 5, 23),
               p.pe.1_cp= 0.73,  p.pe.0_cp= 0.60, p.er.1 = 0.60,
               p.er.0 = 0.60, p.pe.1= 0.60, p.pe.0= 0.60,
```

```
                log.OR.1= 7.4, log.OR.0 = 4.1, alternative = c("greater"),
                alpha = 0.025, method = c("analytical"),
                cutoff = 0.50, n.simqk = 200,
                n.trials = 50, ni.margin = 0)

# Examine results
plot(fit)
```

`sim.Ecp` *The expected conditional power is calculated for each simulated interim dataset.*

Description

Calculates the expected conditional power for each simulated interim dataset. Interim data are simulated based on the probabilities to achieve a favorable early outcome, a favorable primary outcome and an assumption about the association, represented by an log odds ratio, between both endpoints. See Ecp for more information on how the expected conditional power is calculated for the simulated interim datasets.

Usage

```
sim.Ecp(n.1, n.0, n.coh1.1, n.coh1.0, n.interim.1, n.interim.0,
        prior.1 = c(0, 0, 0, 0), prior.0 = c(0, 0, 0, 0),
        p.pe.1_cp = NULL, p.pe.0_cp = NULL,
        p.er.1, p.er.0, p.pe.1, p.pe.0,
        log.OR.1, log.OR.0, alternative = c("greater"), alpha = 0.025,
        method = c("analytical"), assumption = c("design"),
        cutoff = 0.50, n.simqk = 2500,
        n.trials = 10000, ni.margin = 0)
```

Arguments

`n.1, n.0` Total number of subjects planned in the experimental/control arm.

`n.coh1.1, n.coh1.0`
Total number of subjects planned in cohort 1 of the experimental/control arm.

`n.interim.1, n.interim.0`
Planned number of subjects with early response data available at the time of the interim analysis in the experimental/control arm.

`prior.1, prior.0`
Summary vector of hypothetical or historical X and Y data in the experimental/control arm:

- early responders ($X = 1$) for whom $Y = 1$,
- early responders ($X = 1$) for whom $Y = 0$,
- early non-responders ($X = 0$) for whom $Y = 1$, and
- early non-responders ($X = 0$) for whom $Y = 0$.

Default c(0, 0, 0, 0), corresponding to non-informative priors based on a 2x2 table with 0.5 in each cell.

`p.pe.1_cp, p.pe.0_cp`
: Assumed design rate to achieve a favorable primary outcome ($Y = 1$) in the experimental/control arm.

`p.er.1, p.er.0` Proportion of subjects achieving a favorable early response in the experimental/control arm.

`p.pe.1, p.pe.0` Proportion of subjects achieving a favorable primary outcome in the experimental/control arm.

`log.OR.1, log.OR.0`
: Log odds ratio between the presence/absence of X (early endpoint) and the presence/absence of Y (primary endpoint) in the experimental/control arm.

`alternative` A character string specifying the alternative hypothesis, must be `"greater"` (default) or `"less"`.

`alpha` One-sided significance level at which the primary hypothesis will be tested. Default 0.025.

`method` A character string specifying the method, must be one of `"simulation"` (default) or `"analytical"`. The `"simulation"`-method calculates the conditional power via simulations, where the `"analytical"`-method approximates the conditional power via analytical expressions following Lan and Wittes using a test statistic with a normal approximation (this would reduce the computational intensity). See details.

`assumption` A character string specifying the assumption under which the (expected) conditional power is calculated, must be one of `"design"` (default) or `"trend"`.

`cutoff` Cutoff at which stopping is recommended as soon as the expected conditional power drops below it. Default 0.50.

`n.simqk` The number of nuisance parameter sets $(P^d_{Y_1|X_1=1}, P^d_{Y_1|X_1=0}, P^d_{Y_0|X_0=1}, P^d_{Y_0|X_0=0})$ sampled from the posterior density (Van Lancker, 2019). Default 2000.

`n.trials` Number of simulated trials (interim datasets). Default 10000.

`ni.margin` Default value of 0 is set to test for superiority; negative values are used for non-inferiority.

Details

The computational resource demand is high when using the `"simulation"`-method; so, using the analytical approximation will reduce the computational intensity. Note: The analytical method is based on the assumption that the ratio of the number of subjects in the experimental arm to the number of subjects in the control arm is equal to the ratio of the number of subjects in the experimental arm of cohort 1 to the number of subjects in the control arm of cohort 1, equal to the ratio of the number of subjects in the experimental arm of cohort 1 to the number of subjects in the control arm of cohort 2 and equal to the ratio of the number of subjects in the experimental arm of cohort 1 to the number of subjects in the control arm of cohort 3. In practice, if the equalities not apply, then the ratios are at least approximately equal by randomization.

Value

An object of class `sim.Ecp` with components,

`ExpectedConditionalPower`
: A `list` containing the expected conditional power for each of the simulated trials.

`powerReduction.cutoff`
: Powerreduction corresponding with the chosen cutoff.

`fraction.cutoff`
: Fraction of expected conditional power values below the chosen cutoff.

`powerReduction.gammas`
: Powerreduction corresponding with cut-off values $0, 0.01, 0.02, \cdots, 0.99, 1$.

`fraction.gammas`
: Fraction of expected conditional power values below $0, 0.01, 0.02, \cdots, 0.99, 1$.

`cutoff`
: The pre-specified cutoff.

`total`
: A `list` containing the following summary vector:

  - number of subjects who achieved a favorable primary outcome ($Y = 1$) in the experimental arm,
  - number of subjects who achieved a favorable primary outcome ($Y = 1$) in the control arm,
  - number of subjects who did not achieve a favorable primary outcome ($Y = 0$) in the experimental arm, and
  - number of subjects who did not achieve a favorable primary outcome ($Y = 0$) in the control arm

  for each trial.

`p.rej_final`
: A vector containing the final p-value for each trial.

See Also

`Ecp`

Examples

```
# Let us assume a futility scenario whereby the proportion of subjects achieving the early
# response is the same as the proportion of subjects achieving the primary outcome.
# The data generating models for efficacy data are then given by:
#
# Group     P(X=1)    P(Y=1)     log(OR)
# Exp.      0.60      0.60        7.4
# Contr.    0.60      0.60        4.1
#
#
# In each of the 5000 simulated trials, 550 subjects are enrolled and interim data was available
# for 220 of these subjects, 120 of them had info on both the early and primary endpoint.
# Data from a previous study
#
# Group      (X=1, Y=1)       (X=1, Y=0)        (X=0, Y=1)         (X=0, Y=0)
# Exp.           43               9                 1                 13
# Contr.         26               12                5                 23
#
# Furthermore, the assumed (design) rates of achieving the primary endpoint are 0.73
# in the experimental group and 0.60 in the control group.

# Simulation study:
fit <- sim.Ecp(n.1= 275, n.0= 275, n.coh1.1 = 60, n.coh1.0 = 60,
               n.interim.1 = 110, n.interim.0 = 110,
               prior.1 = c(43, 9, 1, 13), prior.0 = c(26, 12, 5, 23),
               p.pe.1_cp= 0.73,  p.pe.0_cp= 0.60, p.er.1 = 0.60,
               p.er.0 = 0.60, p.pe.1= 0.60, p.pe.0= 0.60,
               log.OR.1= 7.4, log.OR.0 = 4.1, alternative = c("greater"),
```

```
                alpha = 0.025, method = c("analytical"),
                cutoff = 0.50, n.simqk = 200,
                n.trials = 50, ni.margin = 0)

# Examine results
summary(fit)
plot(fit)
```

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