Package 'CompAREdesign'

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Title Statistical Functions for the Design of Studies with Composite Endpoints

Version 1.7

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Description It has been designed to calculate the required sample size in randomized clinical trials with composite endpoints. This package also includes functions to calculate the probability of observing the composite endpoint and the expected effect on the composite endpoint, among others. The methods implemented can be found in Bofill & Gómez (2019) <doi:10.1002/sim.8092> and Gómez & Lagakos (2013) <doi:10.1002/sim.5547>.

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ARE_cbe *ARE method for composite binary endpoints*

Description

The composite endpoint is assumed to be a binary endpoint formed by a combination of two events (E1 and E2). We assume that the endpoint 1 is more relevant for the clinical question than endpoint 2. This function calculates the ARE method for binary endpoints. The method quantifies the differences in efficiency of using the composite or the relevant as primary endpoint to lead the trial and, moreover, provides a decision rule to choose the primary endpoint. If the ARE is larger than 1, the composite endpoint may be considered the best option as primary endpoint. Otherwise, the relevant endpoint is preferred.

Usage

```
ARE_cbe(
  p0_e1,
  p0_e2,
  eff_e1,
  effm_e1 = "or",
  eff_e2,
  effm_e2 = "or",
  effm_ce = "or",
  rho
)
```

Arguments

p0_e1	numeric parameter, probability of occurrence E1 in the control group
p0_e2	numeric parameter, probability of occurrence E2 in the control group
eff_e1	numeric parameter, anticipated effect for the composite component E1
effm_e1	Effect measure used for the event E1 (effm_e1 = "diff" for difference of proportions, effm_e1 = "rr" for risk ratio, effm_e1 = "or" for odds ratio)
eff_e2	numeric parameter, anticipated effect for the composite component E2
effm_e2	Effect measure used for the event E2 (effm_e2 = "diff" for difference of proportions, effm_e2 = "rr" for risk ratio, effm_e2 = "or" for odds ratio)
effm_ce	Effect measure used for the composite endpoint (effm_ce = "diff" for difference of proportions, effm_ce = "rr" for risk ratio, effm_ce = "or" for odds ratio)
rho	numeric parameter, Pearson's correlation between the two events E1 and E2

Details

The input parameters stand for the probability of the composite components and Pearson's correlation between the two components. Note that Pearson's correlation takes values between two bounds that depend on the probabilities p0_e1 and p0_e2. To calculate the correlation bounds you can use the R functions lower_corr and upper_corr, available in this package.

Value

Returns the ARE value. If the ARE value is larger than 1 then the composite endpoint is preferred over the relevant endpoint. Otherwise, the endpoint 1 is preferred as the primary endpoint of the study.

References

Bofill Roig, M., & Gomez Melis, G. (2018). Selection of composite binary endpoints in clinical trials. Biometrical Journal, 60(2), 246-261. https://doi.org/10.1002/bimj.201600229

`effectsize_cbe` *Effect for composite binary endpoints*

Description

This function calculates different effect measures for binary composite outcomes. The composite endpoint is assumed to be a binary endpoint formed by a combination of two events (E1 and E2). The effect size is calculated on the basis of anticipated information on the composite components and the correlation between them. The function allows to compute the effect size in terms of the risk difference, risk ratio and odds ratio.

Usage

```
effectsize_cbe(
  p0_e1,
  p0_e2,
  eff_e1,
  effm_e1,
  eff_e2,
  effm_e2,
  effm_ce = "diff",
  rho
)
```

Arguments

`p0_e1`	numeric parameter, probability of occurrence E1 in the control group
`p0_e2`	numeric parameter, probability of occurrence E2 in the control group
`eff_e1`	numeric parameter, anticipated effect for the composite component E1
`effm_e1`	Effect measure used for the event E1 (effm_e1 = "diff" for difference of proportions, effm_e1 = "rr" for risk ratio, effm_e1 = "or" for odds ratio)
`eff_e2`	numeric parameter, anticipated effect for the composite component E2
`effm_e2`	Effect measure used for the event E2 (effm_e2 = "diff" for difference of proportions, effm_e2 = "rr" for risk ratio, effm_e2 = "or" for odds ratio)
`effm_ce`	Effect measure used for the composite endpoint (effm_ce = "diff" for difference of proportions, effm_ce = "rr" for risk ratio, effm_ce = "or" for odds ratio)
`rho`	numeric parameter, Pearson's correlation between the two events E1 and E2

Details

The input parameters stand for the probability of the composite components and Pearson's correlation between the two components. Note that Pearson's correlation takes values between two bounds that depend on the probabilities p0_e1 and p0_e2. To calculate the correlation bounds you can use the R functions lower_corr and upper_corr, available in this package.

Value

Returns the effect for the composite binary endpoint and the effects for the composite components.

References

Bofill Roig, M., & Gómez Melis, G. (2019). A new approach for sizing trials with composite binary endpoints using anticipated marginal values and accounting for the correlation between components. Statistics in Medicine, 38(11), 1935-1956. https://doi.org/10.1002/sim.8092

`effectsize_tte` *Effect for composite time-to-event endpoints*

Description

This function calculates different effect measures for time-to-event composite outcomes. The composite endpoint is assumed to be a time-to-event endpoint formed by a combination of two events (E1 and E2). The effect size is calculated on the basis of anticipated information on the composite components and the correlation between them. Marginal distributions are assumed for m The function allows to compute the effect size in terms of the geometric average hazard ratio, the average hazard ratio, the ratio of restricted mean survival times and the median survival time ratio.

Usage

```
effectsize_tte(
  p0_e1,
  p0_e2,
  HR_e1,
  HR_e2,
  beta_e1 = 1,
  beta_e2 = 1,
  case,
  copula = "Frank",
  rho = 0.3,
  rho_type = "Spearman",
  subdivisions = 1000,
  plot_HR = FALSE
)
```

Arguments

p0_e1	numeric parameter between 0 and 1, expected proportion of observed events for the endpoint E1
p0_e2	numeric parameter between 0 and 1, expected proportion of observed events for the endpoint E2
HR_e1	numeric parameter between 0 and 1, expected cause specific hazard Ratio the endpoint E1
HR_e2	numeric parameter between 0 and 1, expected cause specific hazard Ratio the endpoint E2
beta_e1	numeric positive parameter, shape parameter (β_1) for a Weibull distribution for the endpoint E1 in the control group. See details for more info.
beta_e2	numeric positive parameter, shape parameter (β_2) for a Weibull distribution for the endpoint E2 in the control group. See details for more info.
case	integer parameter in 1,2,3,4 1: none of the endpoints is death 2: endpoint 2 is death 3: endpoint 1 is death 4: both endpoints are death by different causes
copula	character indicating the copula to be used: "Frank" (default), "Gumbel" or "Clayton". See details for more info.
rho	numeric parameter between -1 and 1, Spearman's correlation coefficient o Kendall Tau between the marginal distribution of the times to the two events E1 and E2. See details for more info.
rho_type	character indicating the type of correlation to be used: "Spearman" (default) or "Tau". See details for more info.
subdivisions	integer parameter greater than or equal to 10. Number of subintervals to estimate the effect size. The default is 1000.
plot_HR	logical. If the HR over time should be displayed. The default is FALSE

Details

Some parameters might be difficult to anticipate, especially the shape parameters of Weibull distributions and those referred to the relationship between the marginal distributions. For the shape parameters (beta_e1, beta_e2) of the Weibull distribution, we recommend to use $\beta_j = 0.5$, $\beta_j = 1$ or $\beta_j = 2$ if a decreasing, constant or increasing rates over time are expected, respectively. For the correlation (rho) between both endpoints, generally a positive value is expected as it has no sense to design an study with two endpoints negatively correlated. We recommend to use $\rho = 0.1$, $\rho = 0.3$ or $\rho = 0.5$ for weak, mild and moderate correlations, respectively. For the type of correlation (rho_type), although two different type of correlations are implemented, we recommend the use of the Spearman's correlation. In any case, if no information is available on these parameters, we recommend to use the default values provided by the function.

All returned expected effect sizes for the composite endpoint should be interpreted in relative terms (treated to control). gAHR and AHR represent the risk reduction that will be achieved with the new therapy, while RMST_ratio and Median_ratio represent the gain in time gain terms until the event.

Value

A list formed by two lists: `effect_size`, which contains the expected treatment effect measures and `measures_by_group`, which contains some measures for each group

`effect_size` list:

`gAHR` geometric Average Hazard Ratio

`AHR` Average Hazard Ratio

`RMST_ratio` Restricted Mean Survival Time Ratio

`Median_ratio` Median Survival Time Ratio

`measures_by_group` list:

`pstar` array with the probability of observing the composite event for each group

`RMST` array with the restricted mean survival time for each group

`Median` array with the median surival time for each group

References

Schemper, M., Wakounig, S., Heinze, G. (2009). The estimation of average hazard ratios by weighted Cox regression. Stat. in Med. 28(19): 2473–2489. doi:10.1002/sim.3623

`lower_corr` *Lower bound for Pearson's Correlation*

Description

Pearson's correlation between two binary outcomes takes values between two bounds defined according to the probabilities of the binary outcomes. This function calculates the lower bound of the correlation based on the probabilities of two binary outcomes.

Usage

```
lower_corr(p_e1, p_e2)
```

Arguments

`p_e1`	numeric parameter, probability of the event E1
`p_e2`	numeric parameter, probability of the event E2

Details

lower_corr returns a numeric value between -1 and 0.

Value

Returns the minimum value that the correlation between the two outcomes can take.

Examples

```
CompAREdesign::lower_corr(p_e1=0.1, p_e2=0.6)
```

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prob_cbe *Probability of composite binary endpoints*

Description

This function calculates the probability of the composite binary endpoint formed by a combination of two events (E1 and E2). This probability is calculated by means of the probabilities of the composite components (E1 and E2) and the correlation between them in terms of Pearson's correlation coefficient.

Usage

```
prob_cbe(p_e1, p_e2, rho)
```

Arguments

p_e1	numeric parameter, probability of the event E1
p_e2	numeric parameter, probability of the event E2
rho	numeric parameter, Pearson's correlation between E1 and E2

Details

The input parameters stand for the probability of the composite components and Pearson's correlation between the two components. Note that Pearson's correlation takes values between two bounds that depend on the probabilities p0_e1 and p0_e2. To calculate the correlation bounds you can use the R functions lower_corr and upper_corr, available in this package.

Value

Returns the probability of the composite endpoint (E1 or E2).

References

Bofill Roig, M., & Gomez Melis, G. (2019). A new approach for sizing trials with composite binary endpoints using anticipated marginal values and accounting for the correlation between components. Statistics in Medicine, 38(11), 1935-1956. https://doi.org/10.1002/sim.8092

Examples

```
CompAREdesign::prob_cbe(p_e1=0.1, p_e2=0.2, rho=0)
```

`samplesize_cbe` *Sample size for composite binary endpoints*

Description

This function calculates the required sample size for trials with a composite binary endpoint as primary endpoint. The primary endpoint is assumed to be a composite binary endpoint formed by a combination of two events (E1 and E2). The sample size is computed to evaluate differences between two groups in terms of the risk difference, risk ratio or odds ratio. The sample size is calculated on the basis of anticipated information on the composite components and the correlation between them.

Usage

```
samplesize_cbe(
  p0_e1,
  p0_e2,
  eff_e1,
  effm_e1,
  eff_e2,
  effm_e2,
  effm_ce = "diff",
  rho,
  alpha = 0.05,
  beta = 0.2,
  unpooled = TRUE
)
```

Arguments

`p0_e1`	numeric parameter, probability of occurrence E1 in the control group
`p0_e2`	numeric parameter, probability of occurrence E2 in the control group
`eff_e1`	numeric parameter, anticipated effect for the composite component E1
`effm_e1`	Effect measure used for the event E1 (effm_e1 = "diff" for difference of proportions, effm_e1 = "rr" for risk ratio, effm_e1 = "or" for odds ratio)
`eff_e2`	numeric parameter, anticipated effect for the composite component E2
`effm_e2`	Effect measure used for the event E2 (effm_e2 = "diff" for difference of proportions, effm_e2 = "rr" for risk ratio, effm_e2 = "or" for odds ratio)
`effm_ce`	Effect measure used for the composite endpoint (effm_ce = "diff" for difference of proportions, effm_ce = "rr" for risk ratio, effm_ce = "or" for odds ratio)
`rho`	numeric parameter, Pearson's correlation between the two events E1 and E2
`alpha`	Type I error
`beta`	Type II error
`unpooled`	Variance estimate used for the sample size calculation ("TRUE" for unpooled variance estimate, and "FALSE" for pooled variance estimate).

Details

The input parameters stand for the probability of the composite components and Pearson's correlation between the two components. Note that Pearson's correlation takes values between two bounds that depend on the probabilities p0_e1 and p0_e2. To calculate the correlation bounds you can use the R functions lower_corr and upper_corr, available in this package.

Value

Return the total sample size for composite binary endpoints based on the anticipated values of the composite components and the association between them in terms of Pearson's correlation.

References

Bofill Roig, M., & Gomez Melis, G. (2019). A new approach for sizing trials with composite binary endpoints using anticipated marginal values and accounting for the correlation between components. Statistics in Medicine, 38(11), 1935-1956. https://doi.org/10.1002/sim.8092

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upper_corr *Upper bound for Pearson's Correlation*

Description

Pearson's correlation between two binary outcomes takes values between two bounds defined according to the probabilities of the binary outcomes. This function calculates the upper bound of the correlation based on the probabilities of two binary outcomes.

Usage

```
upper_corr(p_e1, p_e2)
```

Arguments

p_e1	numeric parameter, probability of the event E1
p_e2	numeric parameter, probability of the event E2

Details

upper_corr returns a numeric value between 0 and 1.

Value

Returns the maximum value that the correlation between the two outcomes can take.

Examples

```
CompAREdesign::upper_corr(p_e1=0.3, p_e2=0.6)
```

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