

Package: eselect (via r-universe)

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Title Adaptive Clinical Trial Designs with Endpoint Selection and Sample Size Reassessment

Version 1.1

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Description Endpoint selection and sample size reassessment for multiple binary endpoints based on blinded and/or unblinded data. Trial design that allows an adaptive modification of the primary endpoint based on blinded information obtained at an interim analysis. The decision rule chooses the endpoint with the lower estimated required sample size. Additionally, the sample size is reassessed using the estimated event probabilities and correlation between endpoints. The implemented design is proposed in Bofill Roig, M., Gómez Melis, G., Posch, M., and Koenig, F. (2022). <doi:10.48550/arXiv.2206.09639>.

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eselect	<i>Endpoint selection and sample size reassessment for composite endpoints based on blinded data</i>
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Description

Endpoint selection and sample size reassessment for composite endpoints based on blinded data. 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 selects between the composite endpoint or the relevant endpoint as the primary endpoint of the study and recalculate the sample size accordingly. The decision criteria to decide between the composite endpoint or the relevant endpoint might be the ratio of the corresponding sample sizes ("SS") or the Asymptotic Relative Efficiency ("ARE"). The algorithm of the function is the following: First, the probabilities of the composite components in the control group and the correlation between them are estimated based on blinded data. Second, using the estimated probabilities and the estimated correlation, the decision criteria is computed and the primary endpoint is selected. Finally, the sample size is recalculated according to the decision.

Usage

```
eselect(db, p0_e1, OR1, p0_e2, OR2, criteria = "SS", alpha = 0.05, beta = 0.2)
```

Arguments

db	matrix 2x2 table (pooled sample)
p0_e1	numeric parameter, probability of occurrence E1 in the control group
OR1	numeric parameter, Odds ratio for the endpoint 1
p0_e2	numeric parameter, probability of occurrence E2 in the control group
OR2	numeric parameter, Odds ratio for the endpoint 2
criteria	decision criteria to choose between the composite endpoint or the endpoint 1 as primary endpoint ("SS": Ratio sample sizes, "ARE": Asymptotic Relative Efficiency).
alpha	Type I error.
beta	Type II error.

Value

This function returns the decision (Decision = 1, meaning the chosen endpoint is the composite endpoint; and Decision = 0, meaning the chosen endpoint is the relevant endpoint) and the sample size according to the decision.

References

Bofill Roig, M., Gómez Melis, G., Posch, M., & Koenig, F. (2022). Adaptive clinical trial designs with blinded selection of binary composite endpoints and sample size reassessment. *Biostatistics* (in press). arXiv e-prints, arXiv-2206 (<https://doi.org/10.48550/arXiv.2206.09639>). Bofill Roig, M., & Gómez Melis, G. "Selection of composite binary endpoints in clinical trials." *Biometrical Journal* 60.2 (2018): 246-261.

Examples

```
# Based on Bofill Roig, M., et al.
# (See supplementary material in https://doi.org/10.48550/arXiv.2206.09639)
p0_e1 = 0.173
p0_e2 = 0.055
p1_e1 = 0.121;
p1_e2 = 0.057;
n1 = 569
n0 = 576
n = n0+n1
p1 = (p0_e1*n0 + p1_e1*n1)/n
p2 = (p0_e2*n0 + p1_e2*n1)/n
p_ce = (0.203*n0 + 0.146*n1)/n
OR1 = 0.7
OR2 = 0.9
x11 = round((p1+p2-p_ce)*n)
x12 = round((p1)*n-x11)
x21 = round((p2)*n- x11)
x22 = round((1-p_ce)*n)
data = matrix(c(x11,x12,x21,x22), nrow = 2 , ncol = 2, byrow = FALSE)
eselect(db=data,p0_e1=0.18,OR1=0.70,p0_e2=0.05,OR2=0.9,criteria="SS",alpha=0.05,beta=0.2)
```

eselectsim

*Simulation trials with endpoint selection and sample size reassessment
for composite endpoints based on blinded data*

Description

This function simulates trials with endpoint selection and sample size reassessment for composite binary endpoints based on blinded data. 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 simulates a trial based on the design parameters and use the algorithm implemented in `eselect()` to select the primary endpoint and recalculate the sample size accordingly.

Usage

```
eselectsim(
  ss_arm,
  p0_e1,
  OR1,
  p0_e2,
  OR2,
  p0_ce,
  p_init = 1,
  criteria = "SS",
  H0_e1 = FALSE,
  H0_e2 = FALSE,
  SS_r = TRUE,
  alpha = 0.05,
  beta = 0.2
)
```

Arguments

ss_arm	numeric parameter, sample size per arm
p0_e1	numeric parameter, probability of occurrence E1 in the control group
OR1	numeric parameter, Odds ratio for the endpoint 1
p0_e2	numeric parameter, probability of occurrence E2 in the control group
OR2	numeric parameter, Odds ratio for the endpoint 2
p0_ce	numeric parameter, probability of occurrence composite endpoint in the control group
p_init	numeric parameter, percentage of sample size used in the interim
criteria	decision criteria to choose between the composite endpoint or the endpoint 1 as primary endpoint ("SS": Ratio sample sizes, "ARE": Asymptotic Relative Efficiency).
H0_e1	Simulate under true null hypothesis for the endpoint E1 (TRUE/FALSE).
H0_e2	Simulate under true null hypothesis for the endpoint E2 (TRUE/FALSE).
SS_r	Sample size reassessment (TRUE/FALSE). If TRUE, in those cases where the sample size is less than the needed for achieving the pre-specified power, additional subjects are added after recalculating the sample size. If FALSE, no more subjects are added in the study.
alpha	Type I error.
beta	Type II error.

Value

This function returns the decision (Decision = 1, meaning the chosen endpoint is the composite endpoint; and Decision = 0, meaning the chosen endpoint is the relevant endpoint) and the statistic to test the primary hypothesis according to the decision.

References

Bofill Roig, M., Gómez Melis, G., Posch, M., & Koenig, F. (2022). Adaptive clinical trial designs with blinded selection of binary composite endpoints and sample size reassessment. *Biostatistics* (in press). arXiv e-prints, arXiv-2206 (<https://doi.org/10.48550/arXiv.2206.09639>).

eselectsim_ub	<i>Simulation trials with endpoint selection and sample size reassessment for composite endpoints based on unblinded data</i>
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Description

This function simulates trials with endpoint selection and sample size reassessment for composite binary endpoints based on unblinded data. 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 simulates a trial based on the design parameters and use the algorithm implemented in `eselect()` to select the primary endpoint and recalculate the sample size accordingly.

Usage

```
eselectsim_ub(
  ss_arm,
  p0_e1,
  OR1,
  p0_e2,
  OR2,
  p0_ce,
  p_init = 1,
  criteria = "SS",
  H0_e1 = FALSE,
  H0_e2 = FALSE,
  SS_r = TRUE,
  alpha = 0.05,
  beta = 0.2
)
```

Arguments

<code>ss_arm</code>	numeric parameter, sample size per arm
<code>p0_e1</code>	numeric parameter, probability of occurrence E1 in the control group
<code>OR1</code>	numeric parameter, Odds ratio for the endpoint 1
<code>p0_e2</code>	numeric parameter, probability of occurrence E2 in the control group
<code>OR2</code>	numeric parameter, Odds ratio for the endpoint 2
<code>p0_ce</code>	numeric parameter, probability of composite endpoint in the control group
<code>p_init</code>	numeric parameter, percentage of sample size used in the interim

criteria	decision criteria to choose between the composite endpoint or the endpoint 1 as primary endpoint ("SS": Ratio sample sizes, "ARE": Asymptotic Relative Efficiency).
H0_e1	Simulate under true null hypothesis for the endpoint E1 (TRUE/FALSE).
H0_e2	Simulate under true null hypothesis for the endpoint E2 (TRUE/FALSE).
SS_r	Sample size reassessment (TRUE/FALSE). If TRUE, in those cases where the sample size is less than the needed for achieving the pre-specified power, additional subjects are added after recalculating the sample size. If FALSE, no more subjects are added in the study.
alpha	Type I error.
beta	Type II error.

Value

This function returns the decision (Decision = 1, meaning the chosen endpoint is the composite endpoint; and Decision = 0, meaning the chosen endpoint is the relevant endpoint) and the statistic to test the primary hypothesis according to the decision.

eselect_ub	<i>Endpoint selection and sample size reassessment for composite endpoints based on unblinded data</i>
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Description

Endpoint selection and sample size reassessment for composite endpoints based on unblinded data. 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 selects between the composite endpoint or the relevant endpoint as the primary endpoint of the study and recalculate the sample size accordingly. The decision criteria to decide between the composite endpoint or the relevant endpoint might be the ratio of the corresponding sample sizes ("SS") or the Asymptotic Relative Efficiency ("ARE"). The algorithm of the function is the following: First, the probabilities of the composite components in the control group and the correlation between them are estimated based on unblinded data. Second, using the estimated probabilities and the estimated correlation, the decision criteria is computed and the primary endpoint is selected. Finally, the sample size is recalculated according to the decision.

Usage

```
eselect_ub(
  db0,
  db1,
  p0_e1,
  OR1,
  p0_e2,
  OR2,
  criteria = "SS",
```

```
    alpha = 0.05,  
    beta = 0.2  
  )
```

Arguments

db0	matrix
db1	matrix
p0_e1	numeric parameter, probability of occurrence E1 in the control group
OR1	numeric parameter, Odds ratio for the endpoint 1
p0_e2	numeric parameter, probability of occurrence E2 in the control group
OR2	numeric parameter, Odds ratio for the endpoint 2
criteria	decision criteria to choose between the composite endpoint or the endpoint 1 as primary endpoint ("SS": Ratio sample sizes, "ARE": Asymptotic Relative Efficiency).
alpha	Type I error.
beta	Type II error.

Value

This function returns the decision (Decision = 1, meaning the chosen endpoint is the composite endpoint; and Decision = 0, meaning the chosen endpoint is the relevant endpoint) and the sample size according to the decision.

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