Adaptive selection of binary composite endpoints and sample size reassessment based on blinded data

Marta Bofill Roig, Guadalupe Gómez Melis, Martin Posch and Franz Koenig

Outline

Introduction

In most clinical trials, the treatment efficacy is characterized by a set of endpoints.

Composite Endpoint: Combination of several responses into a unique variable.[1]

Advantages:

- More information
- Power might be increased
- No need for an adjustment for multiplicity

Disadvantages:

- Difficult to anticipate the design parameters
- Challenging interpretation of results

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Planning of the sample size becomes complex due to the different effects and event rates across components and due to the correlation between them.

! Components may be of different relevance.

! The correlation between endpoints is usually not reported.

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Goal:

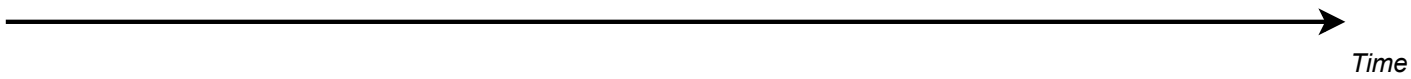
Adaptive design which selects between the composite endpoint or its most relevant component as primary endpoint and recalculates the sample size accordingly.

Adaptive designs with endpoint selection

Adaptive design with endpoint selection and sample size reassessment

Endpoints of interest:

- Primary composite endpoint $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$
- Main relevant endpoint ε_1



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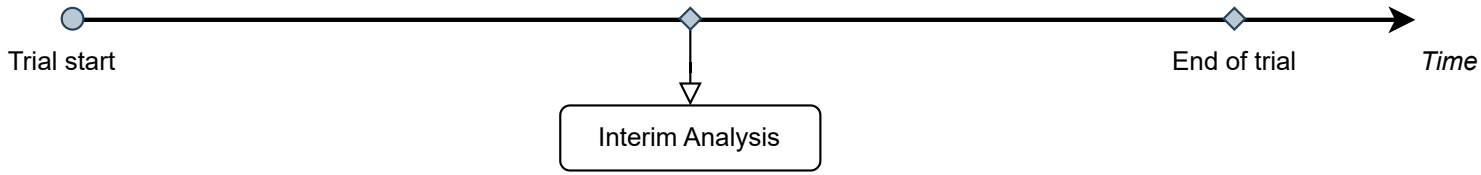

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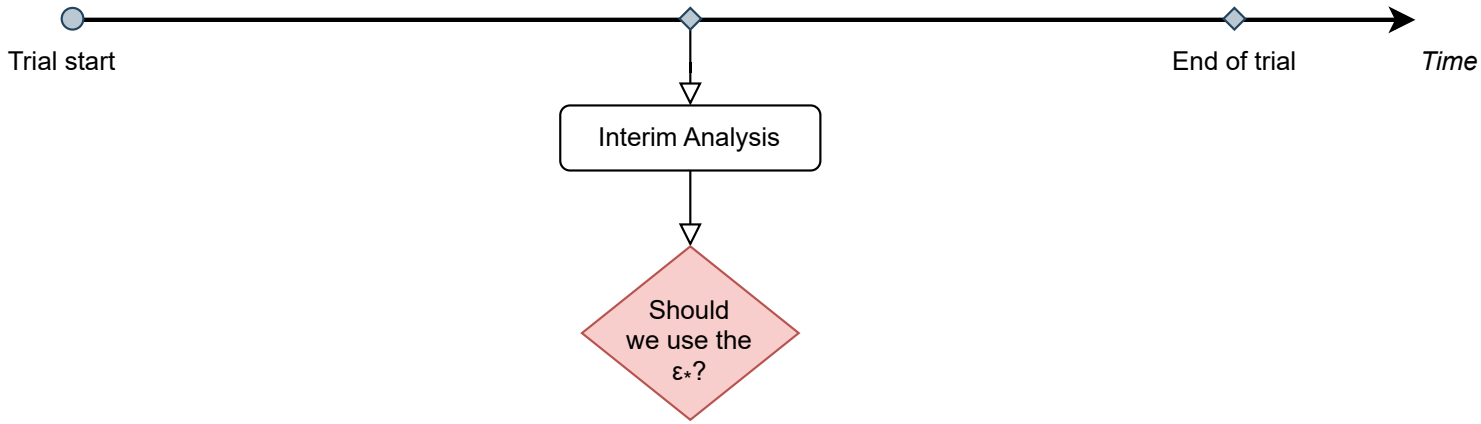

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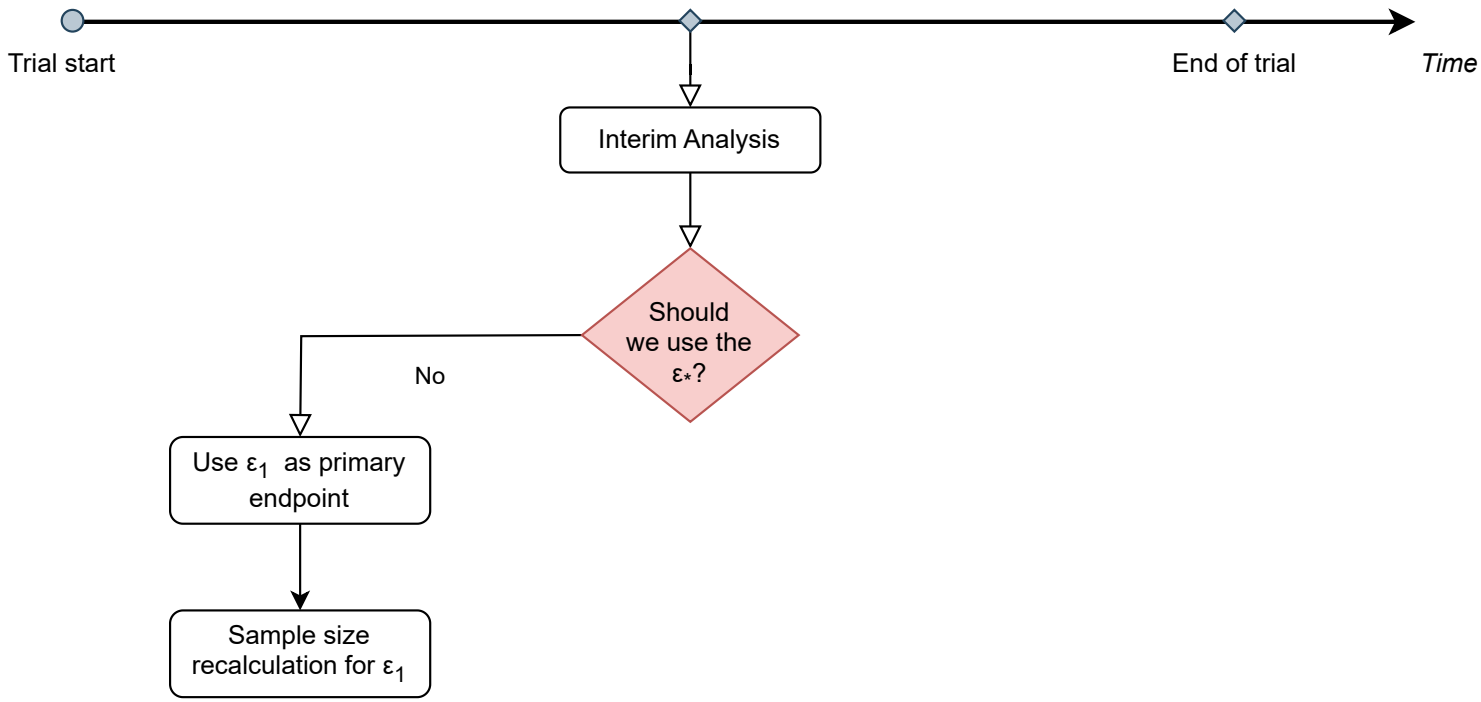

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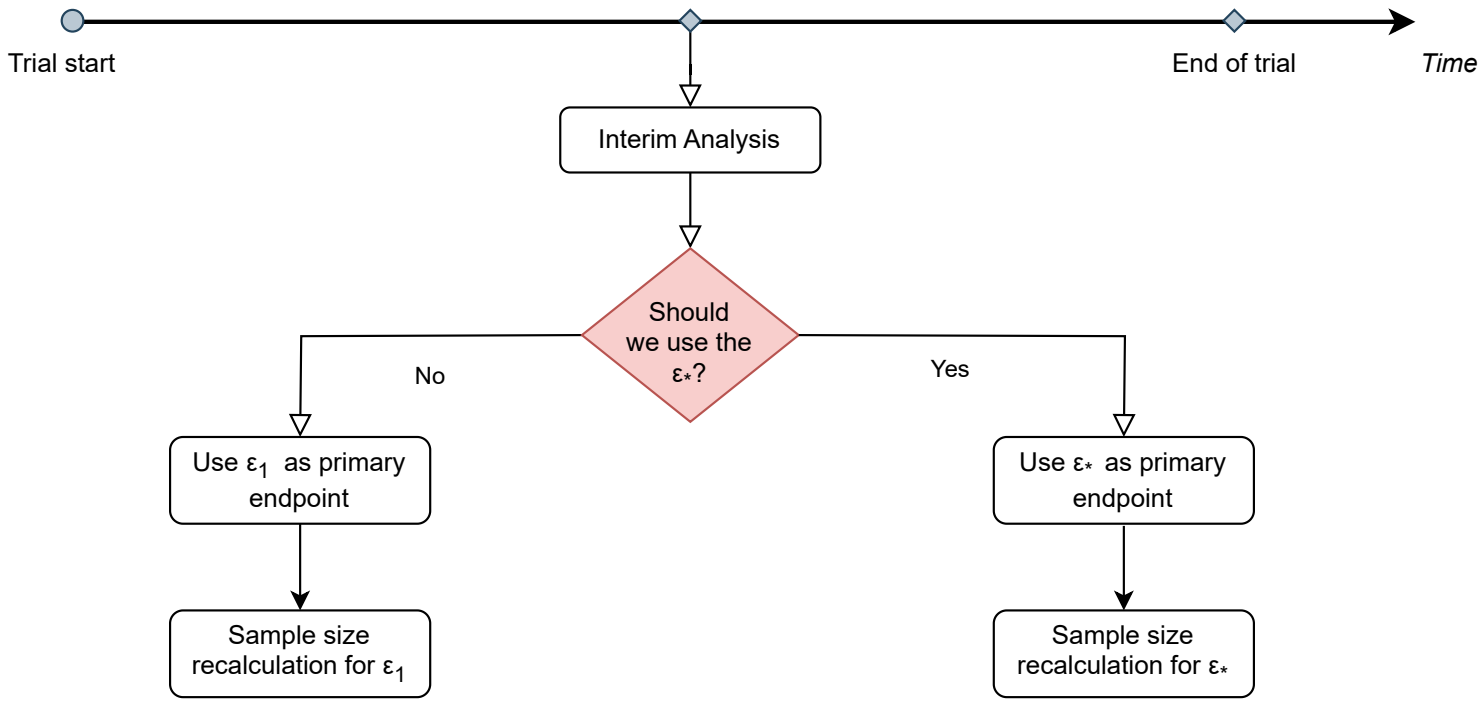

How to define the decision rule and how to recalculate the sample size?

Basic Notation

- Control Group $= 0$
- Treatment Group $= 1$

Primary Endpoint	**Binary Response**	**Probabilities**	**Odds Ratio**	**Sample Size**
ε_1	X_1	$(p_1^{(0)}, p_1^{(1)})$	OR_1	N_1
ε_2	X_2	$(p_2^{(0)}, p_2^{(1)})$	OR_2	N_2
$\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$	$X_* = \begin{cases} 1, & \text{if } X_1 + X_2 \geq 1 \\ 0, & \text{if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	OR_*	N_*

Initial design Composite endpoint's parameters based on its components

Primary composite endpoint ε_*:

$$\mathcal{H}_* : \begin{cases} H_0 : & \log(\mathrm{OR}_*) = 0 \\ H_1 : & \log(\mathrm{OR}_*) < 0 \end{cases}$$

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Designing the trial based on components' parameters[2]

Event rates under the control group ($i = 0$):

$$p_*^{(i)} = 1 - q_1^{(i)} q_2^{(i)} - \rho\sqrt{p_1^{(i)} p_2^{(i)} q_1^{(i)} q_2^{(i)}}$$

where $q_k^{(i)} = 1 - p_k^{(i)}$;

Odds ratio:

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Sample size:

$$N_*(p_*^{(0)}, OR_*) = \left(\frac{z_\alpha + z_\beta}{\log(OR_*)}\right)^2 \cdot \left(\frac{1}{p_*^{(0)}(1 - p_*^{(0)})} + \frac{1}{p_*^{(1)}(1 - p_*^{(1)})}\right)$$

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Sample size:

$$N_*(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, \rho)$$

Initial design assuming correlation equal 0:

$$N_*(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, 0) \leq N_*(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, \rho)$$

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Decision rule How to select the primary endpoint?

Select the primary endpoint at interim stage:

Primary composite endpoint ε_*:	Primary endpoint ε_1:
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Decision rule to select the primary endpoint:

$$d(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, \rho) \quad = \quad \frac{N_1(p_1^{(0)}, OR_1)}{N_*(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, \rho)}$$

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Criterion

- $d(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, \rho) > 1 \Longrightarrow$ composite endpoint ε_* as primary endpoint.
- $d(p_1^{(0)}, p_2^{(0)}, OR_1, OR_2, \rho) \leq 1 \Longrightarrow$ relevant endpoint ε_1 as primary endpoint.

How to calculate the decision rule based on blinded data?

How to estimate $d(\cdot)$ based on information obtained at an interim stage?

(i) Estimate the observed responses in the pooled sample:

$$p_k = \pi p_k^{(0)} + (1-\pi) p_k^{(1)} \qquad \text{for } k = 1, 2, *$$

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(iv) Compute correlation estimator:

$$\hat{\rho} = \frac{(n^{(0)} + n^{(1)})\hat{p}_* - n^{(0)}(1 - \hat{q}_1^{(0)}\hat{q}_2^{(0)}) - n^{(1)}(1 - \hat{q}_1^{(1)}\hat{q}_2^{(1)})}{-n^{(0)}\sqrt{\hat{p}_1^{(0)}\hat{p}_2^{(0)}\hat{q}_1^{(0)}\hat{q}_2^{(0)}} - n^{(1)}\sqrt{\hat{p}_1^{(1)}\hat{p}_2^{(1)}\hat{q}_1^{(1)}\hat{q}_2^{(1)}}}$$

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(v) Compute the decision rule using the estimated probabilities and correlation:

$$d(\hat{p}_1^{(0)}, \hat{p}_2^{(0)}, OR_1, OR_2, \hat{\rho})$$

Adaptive modification on the primary endpoint and sample size reassessment

If $d(\hat{p}_1^{(0)}, \hat{p}_2^{(0)}, OR_1, OR_2, \hat{\rho}) > 1$:

Primary composite endpoint ε_*:

$$\mathcal{H}_* : \begin{cases} H_0 : & \log(\text{OR}_*) = 0 \\ H_1 : & \log(\text{OR}_*) < 0 \end{cases}$$

Trial reassessment:

- Event rate: $\hat{p}_*^{(0)}(\hat{p}_1^{(0)}, \hat{p}_2^{(0)}, \hat{\rho})$
- Expected effect size: $\text{OR}_*(\hat{p}_1^{(0)}, \hat{p}_2^{(0)}, OR_1, OR_2, \hat{\rho})$
- Sample size: $N_*(\hat{p}_1^{(0)}, \hat{p}_2^{(0)}, OR_1, OR_2, \hat{\rho})$
- Sample size reassessment: $\max(n, N_*)$

If $d(\hat{p}_1^{(0)}, \hat{p}_2^{(0)}, OR_1, OR_2, \hat{\rho}) \leq 1$:

Primary endpoint ε_1:

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Trial reassessment:

- Event rate: $\hat{p}_1^{(0)}$
- Expected effect size: OR_1
- Sample size: $N_1(\hat{p}_1^{(0)}, \text{OR}_1)$
- Sample size reassessment: $\max(n, N_1)$

Simulation study

Simulation study design

Two-arm trial with two binary endpoints:

- Probability ε_1 control group ($p_1^{(0)}$): $0.1, 0.2$;
- Probability ε_2 control group ($p_2^{(0)}$): $0.1, 0.25$;
- Odds ratio ε_1 (OR_1): $0.6, 0.8$;
- Odds ratio ε_2 (OR_2): $0.75, 0.8$;
- Correlation between endpoints (ρ): $0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8$;

Number of replicates: 100 000

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Objetives

- Compare the statistical power using the composite endpoint, using the relevant endpoint, or the *selected endpoint*.
- Evaluate the type I error in the adaptive design.

Simulation results without sample size reassessment

- Endpoint selection at the end of the trial (100% of total sample size)
- Sample size calculated to have 0.80 power to detect an effect of OR_1 on ε_1 at significance level $\alpha = 0.05$.

Under H_1:

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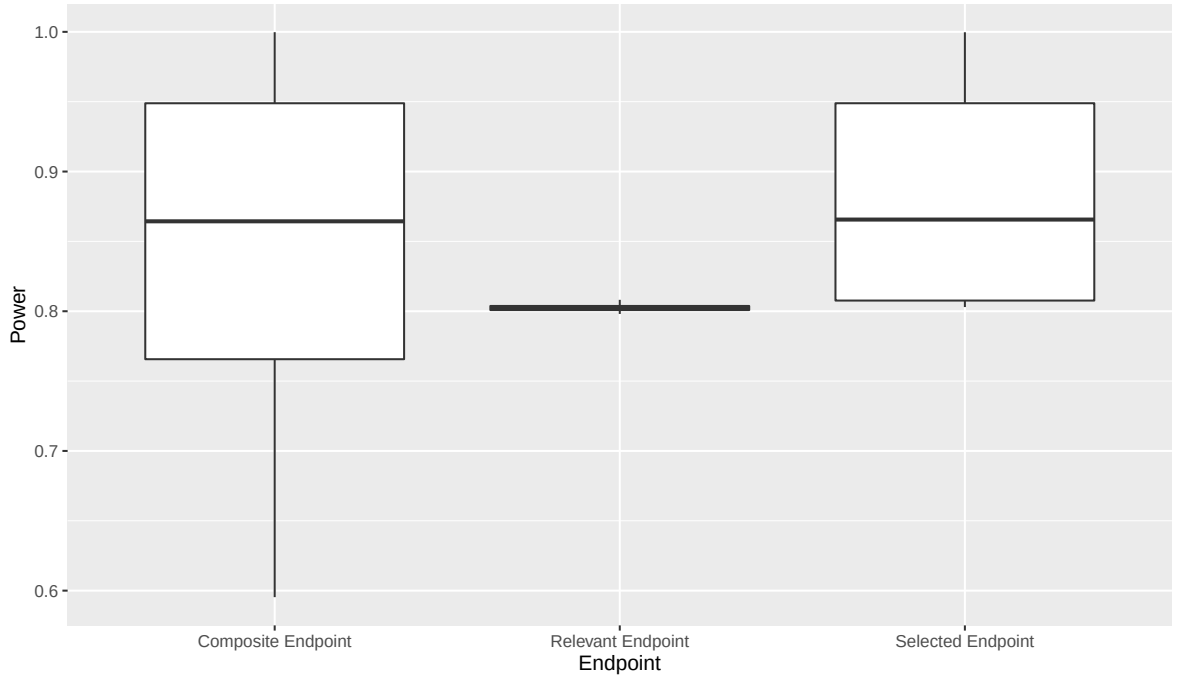

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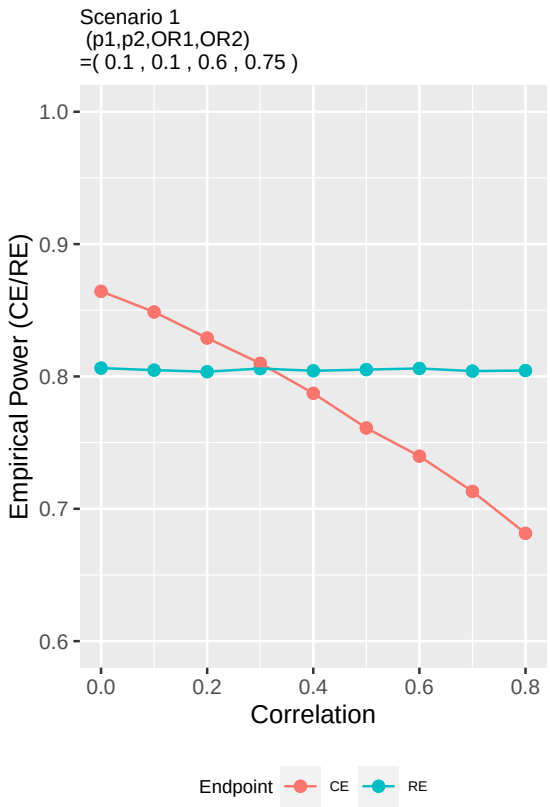

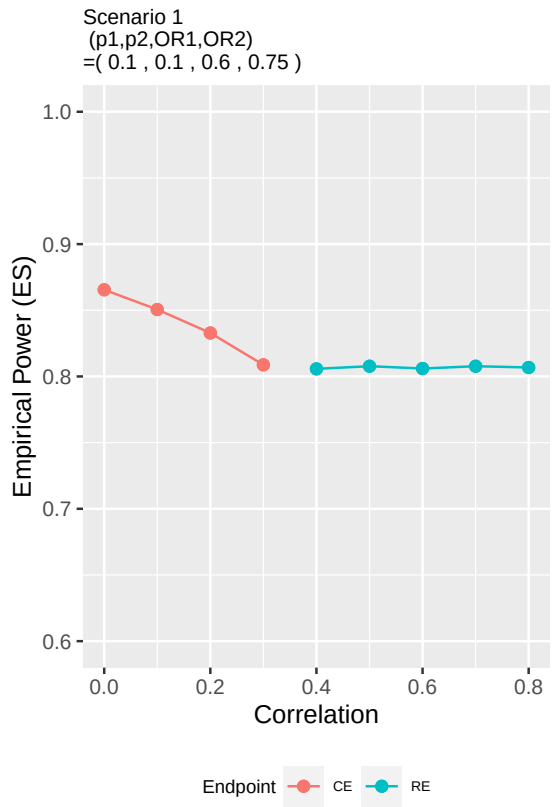

Correlation	Decision rule	% Composite Endpoint
0	1.21	100
0.1	1.14	100
0.2	1.08	99.54
0.3	1.02	71.79
0.4	0.96	9.94
0.5	0.9	0.12
0.6	0.84	0
0.7	0.78	0
0.8	0.72	0

Simulation results with sample size reassessment

- Endpoint selection at interim analysis with 50% of total sample size
- Initial sample size calculated to have 0.80 power to detect an effect of OR_* on ε_* at significance level $\alpha = 0.05$ (assuming $\rho = 0$).

Under H_1:

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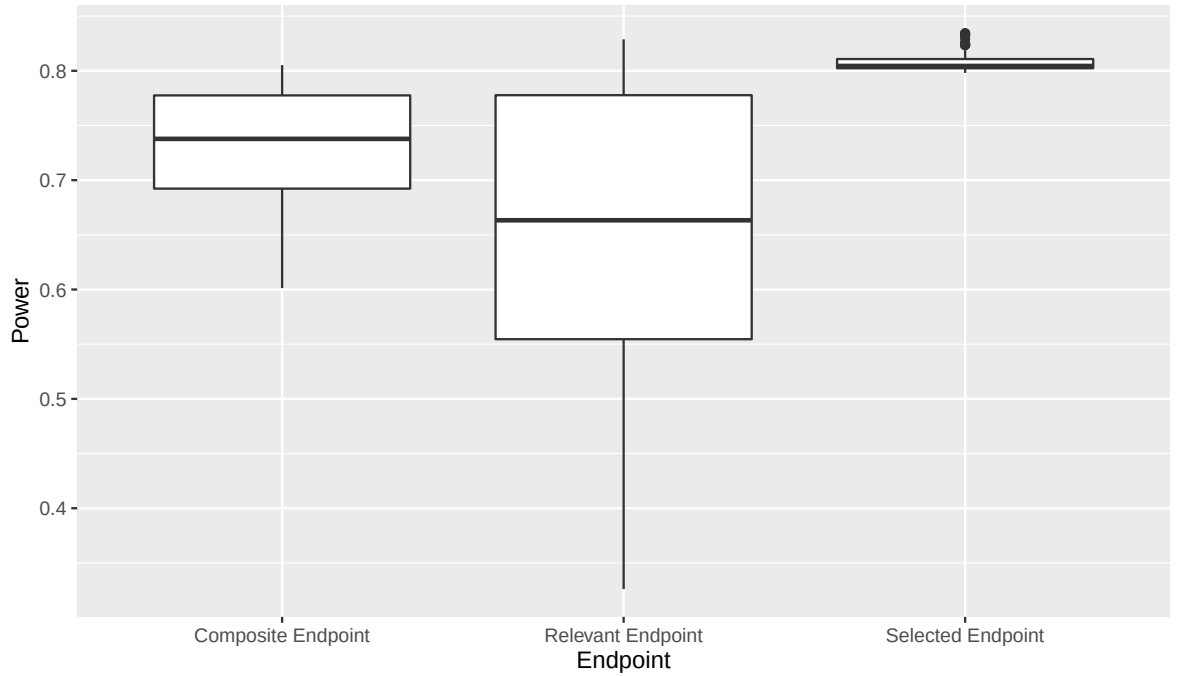

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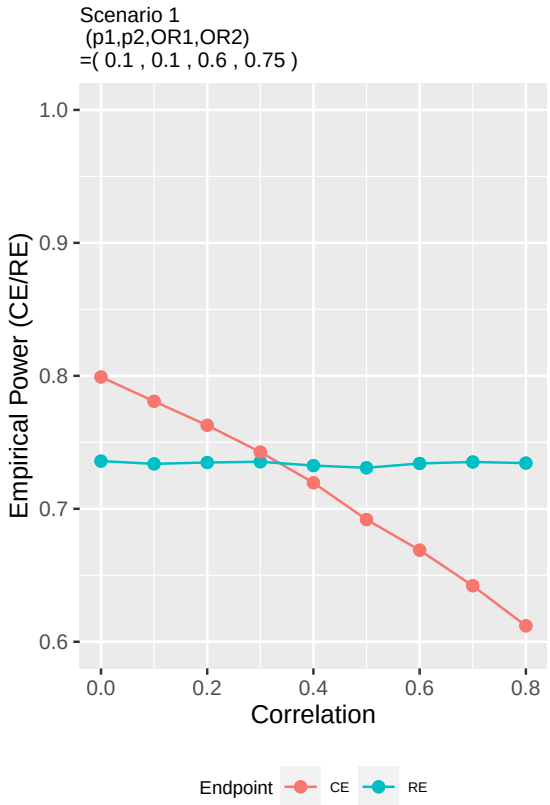

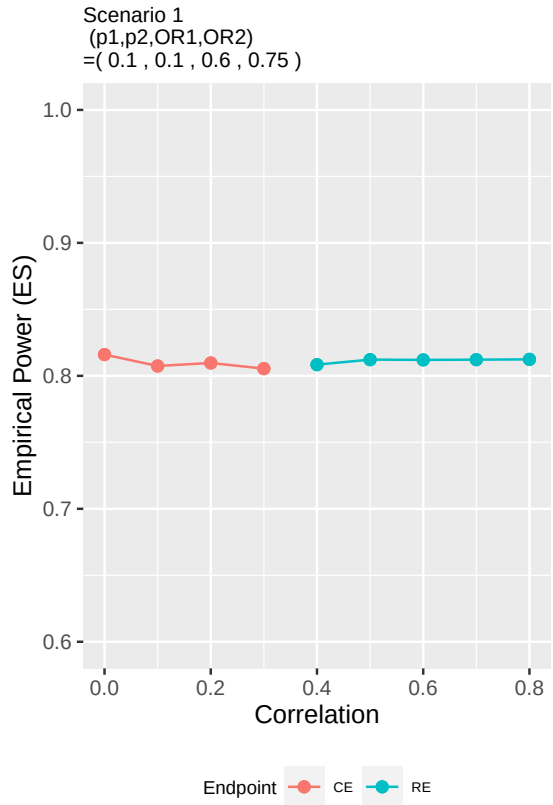

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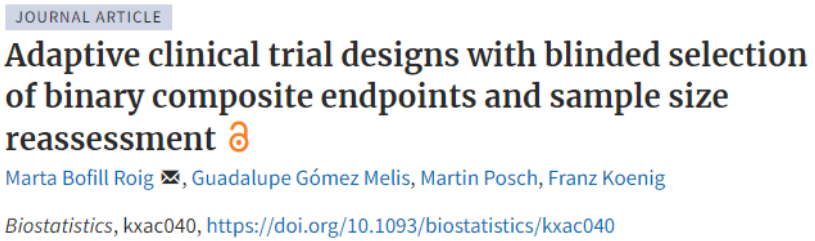
- Design that allows an adaptive modification of the primary endpoint based on information obtained at an interim analysis.
  - Equally or more powerful than designs without adaptive modification.
  - The targeted power is achieved even if the correlation is misspecified.
  - Type I error is maintained due to blinded adaptation rules.
- Extension for more than two composite components and more than two arms.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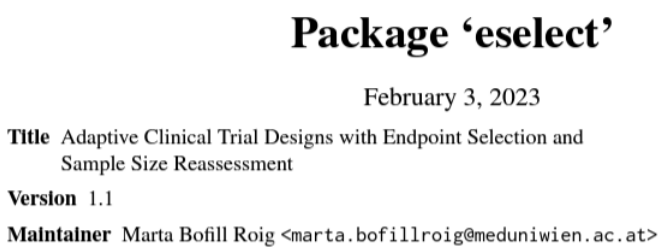
Package 'eselect'

February 3, 2023

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

Version 1.1

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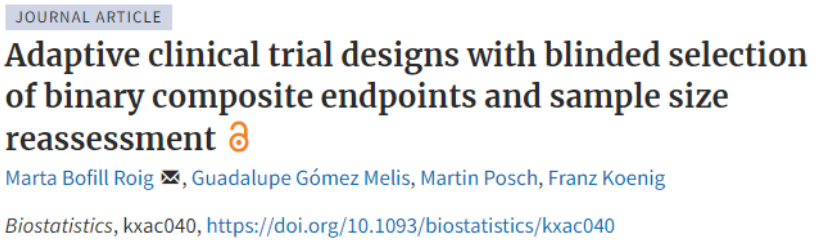
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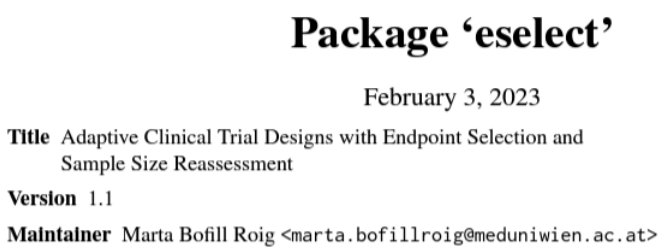
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Future research:

- Adaptive design for multiple endpoints and different comparisons.
- Extension for time-to-event composite endpoints.

Thank you very much for your attention!