

# Sample Size derivation for Binary Composite Endpoints

Marta Bofill Roig  
Guadalupe Gómez Melis



UNIVERSITAT POLITÈCNICA  
DE CATALUNYA  
BARCELONATECH



# Primary Composite Endpoints

## Efficacy endpoints

The primary endpoint measures the clinical evidence in a clinical trial.

- Reporting more than one efficacy endpoints.

## Composite Endpoint

Combination of several responses into a unique variable.

- More information.
- Power might be increased.

## Issues when planning clinical trials with Composite Endpoints:

- How to specify the treatment effect.
- To determine the required sample size.
- Interpretation of the results.

# Outline

**1** Treatment Effect specification

**2** Sample Size derivation

**3** Interpretation of the results

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# Coronary artery disease (TAXUS-V<sup>1</sup>)

- Control group = 0
- Treatment group = 1

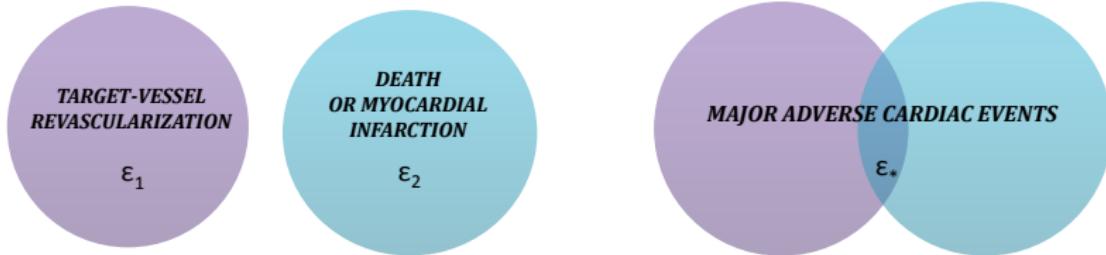
Event	Binary Response	Probabilities	Odds Ratio
Target vessel revascularization $\varepsilon_1$	$X_1$	$(p_1^{(0)}, p_1^{(1)})$	$OR_1$
Death or Myocardial infarction $\varepsilon_2$	$X_2$	$(p_2^{(0)}, p_2^{(1)})$	$OR_2$

<sup>1</sup> Stone GW, et al.; TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. JAMA. 2005 Sep 14; 294(10):1215–23.

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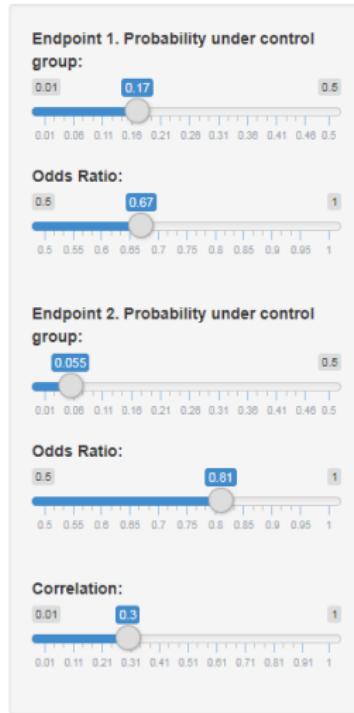
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Major adverse cardiac events $\varepsilon_*$	$X_* = \begin{cases} 1, & \text{if } X_1 + X_2 \geq 1 \\ 0, & \text{if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$OR_*$



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# CompARE : Binary Endpoints

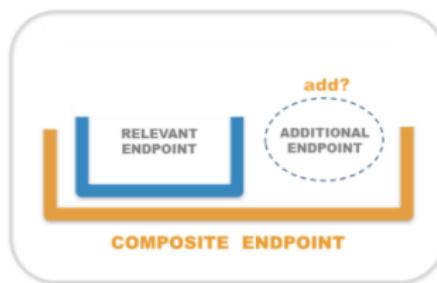


Home      Correlation Bounds      ARE value      Difference in proportions  
Computation of OR\*      Sample Size      Recommendations      Help

## Welcome to Compare platform.

This website will help you to:

- \* Analyze whether you should use a Composite Endpoint as Primary endpoint.
- \* Sample size for Composite Binary Endpoint.
- \* Compare different scenarios depending on your candidate endpoints.
- \* Get helpful numerical and intuitive graphical results.



<https://matabofillroig.shinyapps.io/shiny/>

# Composite Binary Endpoint from its margins

Event	Binary Response	Probabilities	Odds	Odds Ratio
$\varepsilon_1$	$X_1$	$(p_1^{(0)}, p_1^{(1)})$	$O_1^{(0)} = p_1^{(0)} / (1 - p_1^{(0)})$	$OR_1$
$\varepsilon_2$	$X_2$	$(p_2^{(0)}, p_2^{(1)})$	$O_2^{(0)} = p_2^{(0)} / (1 - p_2^{(0)})$	$OR_2$
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Probability of  $\varepsilon_*$  (Bahadur's Theorem<sup>2</sup>):

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

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Odds Ratio of  $\varepsilon_*$ <sup>3</sup>:

$$OR_* = \frac{\left( (1 + OR_1 O_1^{(0)}) (1 + OR_2 O_2^{(0)}) - 1 - \rho^{(1)} \sqrt{OR_1 OR_2 O_1^{(0)} O_2^{(0)}} \right)}{\left( (1 + O_1^{(0)}) (1 + O_2^{(0)}) - 1 - \rho^{(0)} \sqrt{O_1^{(0)} O_2^{(0)}} \right)} \cdot \frac{1 + \rho^{(0)} \sqrt{O_1^{(0)} O_2^{(0)}}}{1 + \rho^{(1)} \sqrt{OR_1 OR_2 O_1^{(0)} O_2^{(0)}}}$$

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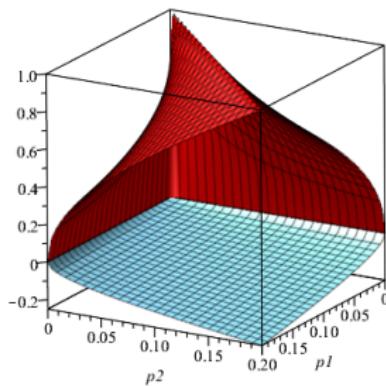
<sup>2</sup>Bahadur R. R. (1961). A representation of the joint distribution of responses to n dichotomous items. Stanford University Press. 158–168.

<sup>3</sup>Bofill M, Gómez G (2017). Selection of composite binary endpoints in clinical trials. *Submitted*.

## Bounds for Pearson's correlations<sup>4</sup> $\rho^{(0)}, \rho^{(1)}$

Given marginal parameters  $\theta = (p_1^{(0)}, p_2^{(0)}, p_1^{(1)}, p_2^{(1)}) \equiv (p_1^{(0)}, p_2^{(0)}, \text{OR}_1, \text{OR}_2)$  the correlations  $\rho^{(0)}, \rho^{(1)}$  are bounded.

$$-1 \leq B_L^{(k)}(\theta) \leq \rho^{(k)} \leq B_U^{(k)}(\theta) \leq 1$$



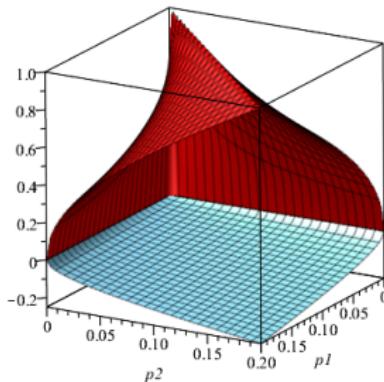
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Assuming  $\rho^{(0)} = \rho^{(1)}$ :

$$B_L(\theta) = \max\{B_L^{(0)}(\theta), B_L^{(1)}(\theta)\} \leq \rho \leq B_U(\theta) = \min\{B_U^{(0)}(\theta), B_U^{(1)}(\theta)\}$$

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Odds ratio bounds when  $\rho^{(0)} = \rho^{(1)}$  given  $\theta = (p_1^{(0)}, p_2^{(0)}, \text{OR}_1, \text{OR}_2)$

How different is the treatment effect in terms of the correlation?

$$\min_{B_L(\theta) \leq \rho \leq B_U(\theta)} \{\text{OR}_*(\rho; \theta)\} \leq \text{OR}_*(\rho; \theta) \leq \max_{B_L(\theta) \leq \rho \leq B_U(\theta)} \{\text{OR}_*(\rho; \theta)\}$$

TAXUS-V: Placitaxel-eluting stent (Intervention) versus Bare metal stents (Control)

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Single Endpoint  $\varepsilon_1 \rightarrow$  Target-vessel revascularization  $p_1^{(0)} = 0.173 \quad \text{OR}_1 = 0.67$

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Single Endpoint  $\varepsilon_2 \rightarrow$  Death or myocardial infarction  $p_2^{(0)} = 0.055 \quad \text{OR}_2 = 0.81$

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Composite Endpoint  $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2 \rightarrow$  Major adverse cardiac events  $p_*^{(0)}(\rho; \theta) \quad \text{OR}_*(\rho; \theta)$

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$$-0.08 = B_L(\theta) \leq \rho \leq B_U(\theta) = 0.53$$

# CompARE : Binary Endpoints

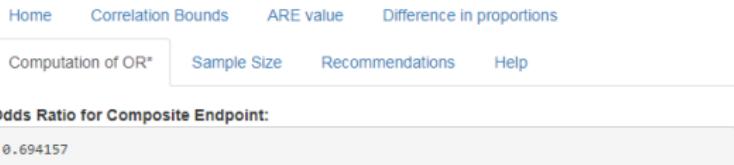
Endpoint 1. Probability under control group:

Odds Ratio:

Endpoint 2. Probability under control group:

Odds Ratio:

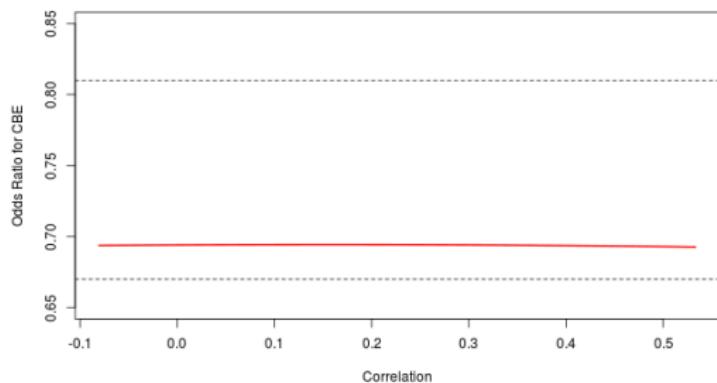
Correlation:



OR\* depending on the correlation

Lower Bound OR\*:  
0.6927195

Upper Bound OR\*:  
0.6943678



If  $p_2^{(0)} < 0.1$ , then  $\text{OR}_*(\rho) \cong \text{OR}_1$ .

If  $p_1^{(0)} < 0.1$ , then  $\text{OR}_*(\rho) \cong \text{OR}_2$ .

If  $p_1^{(0)}, p_2^{(0)} > 0.1$ , then  $\text{OR}_*(\rho)$  depends on the correlation.

# Outline

**1** Treatment Effect specification

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# Sample Size for Composite Binary Endpoints

Our problem:

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

Sample Size derivation for composite endpoints:

$$n_*(p_1^{(0)}, p_2^{(0)}, \text{OR}_1, \text{OR}_2, \rho) = 2 \cdot \left( \frac{z_\alpha + z_\beta}{\log(\text{OR}_*)} \right)^2 \cdot \left( \frac{1}{p_*^{(1)} q_*^{(1)}} + \frac{1}{p_*^{(0)} q_*^{(0)}} \right)$$

- Sample size behavior in terms of  $\theta = (p_1^{(0)}, p_2^{(0)}, \text{OR}_1, \text{OR}_2)$  and  $\rho$ .

# Sample Size for Composite Endpoints given $\theta = (p_1^{(0)}, p_2^{(0)}, \text{OR}_1, \text{OR}_2)$

For  $\rho^{(0)} = \rho^{(1)}$ , the sample size **increases** and **is bounded** according to  $\rho$ :

$$n_*(B_L(\theta); \theta) \leq n_*(\rho; \theta) \leq n_*(B_U(\theta); \theta)$$

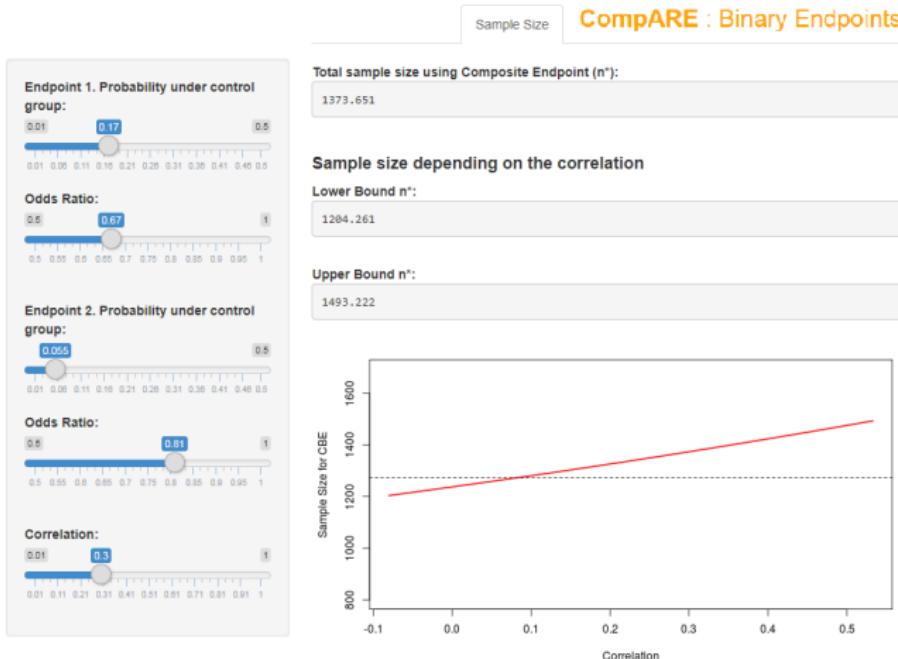
## Approaches for Sample Size derivation involving composite endpoints with:

- (I) Non-information on the correlation.
- (II) Partial-information on the correlation.

**Conservative approach:** Use the upper bound, that is,  $n_*(B_U(\theta); \theta)$ .

# Sample Size derivation with non-information on the correlation

**Conservative approach:** Use the upper bound, that is,  $n_*(B_U(\theta); \theta)$ . ( $\alpha = 0.05, \beta = 0.2$ )



# Sample Size derivation with partial-information on the correlation

**Classify correlation strengths:**  $\rho_w \equiv$  Weak,  $\rho_m \equiv$  Moderate,  $\rho_s \equiv$  Strong.

- $\rho_w \equiv$  Weak

$$n_*(B_L^w(\theta); \theta) \leq n_*(\rho_w; \theta) \leq \textcolor{red}{n_*(B_U^w(\theta); \theta)}$$

- $\rho_m \equiv$  Moderate

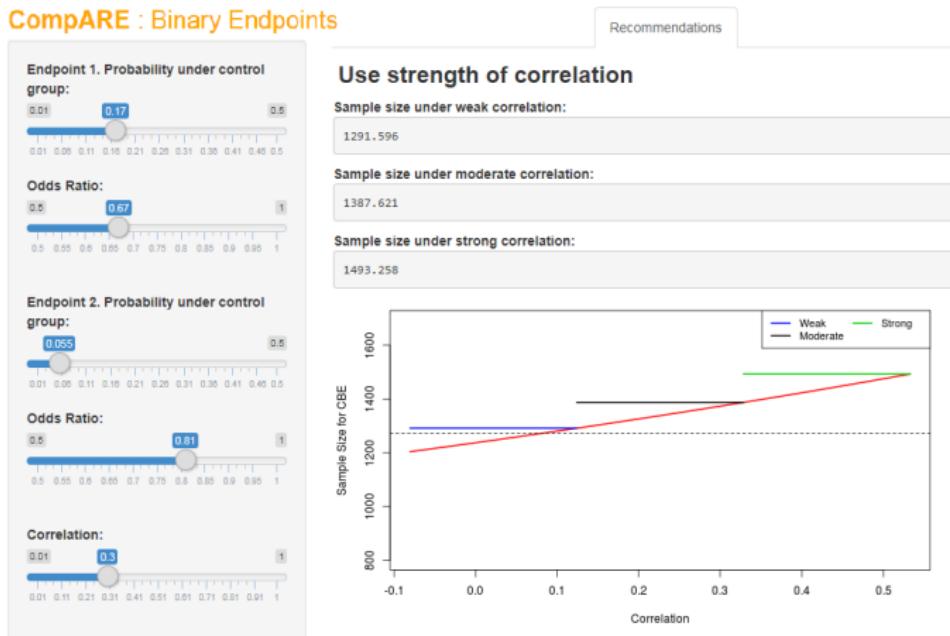
$$n_*(B_L^m(\theta); \theta) \leq n_*(\rho_m; \theta) \leq \textcolor{red}{n_*(B_U^m(\theta); \theta)}$$

- $\rho_s \equiv$  Strong

$$n_*(B_L^s(\theta); \theta) \leq n_*(\rho_s; \theta) \leq \textcolor{red}{n_*(B_U^s(\theta); \theta)}$$

# Sample Size derivation with partial-information on the correlation

**Classify correlation strengths:**  $\rho_w \equiv$  Weak,  $\rho_m \equiv$  Moderate,  $\rho_s \equiv$  Strong.  
 $(\alpha = 0.05, \beta = 0.2)$



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## What are the clinical implications?: Interpretation of the results

**Relationship between treatment effects when  $\rho^{(0)} = \rho^{(1)}$ :**

$$\text{OR}_1 = \text{OR}_2 = 1 \quad \Rightarrow \quad \text{OR}_* = 1$$

**Identifiability problem:**

$$\text{OR}_* = 1 \quad \not\Rightarrow \quad \text{OR}_1 = 1, \text{ OR}_2 = 1$$

Example:

- Non-treatment effect for target vessel revascularization:  $\text{OR}_1 = 1$ .
- Treatment effect for death or MI:  $\text{OR}_2 = 0.6$ .

$$0.9 \leq \text{OR}_*(\rho) \leq 0.95$$

# Concluding remarks and future research

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## Future Research

- Behavior of the type I error rate and power under misspecification of the correlation.
- Adaptive designs for Sample Size derivation with Composite Binary Endpoints.
- Improving the implementation in the web platform and Shiny application *CompARE*.

A word cloud centered around the words "thank you" in various languages. The words are arranged in a cluster, with "thank" at the top left and "you" at the bottom right. The background is white, and the words are in different colors. Some words have their phonetic pronunciation written below them.

Key words and their phonetic pronunciations:

- danke 謝謝 (rakhmat)
- спасибо (spasib)
- Баярлалаа (faafetai lava)
- спасибо (killos dankie)
- дханявад (dhanavad)
- спасибо (kesetom)
- спасибо (enkosi)
- спасибо (bedankt)
- спасибо (hvala)
- спасибо (mautuu)
- спасибо (sobodi)
- спасибо (dekuji)
- спасибо (obrigado)
- спасибо (mesi)
- спасибо (najis tuke)
- спасибо (sagoluu)
- спасибо (didi nadoba)
- спасибо (kam sah hamida)
- спасибо (তোমাকে ধন্যবাদ)
- спасибо (감사합니다)
- спасибо (xiexie)
- спасибо (ευχαριστώ)
- спасибо (merci)
- спасибо (ngiyabonga)
- спасибо (teşekkür ederim)
- спасибо (gracias)
- спасибо (tak)
- спасибо (raibh)
- спасибо (maith agat)
- спасибо (arigatō)
- спасибо (dakujem)
- спасибо (trugarez)
- спасибо (mercs)
- спасибо (xwala)
- спасибо (asanle)
- спасибо (manana)
- спасибо (obrigada)
- спасибо (mochchakkeram)
- спасибо (djiere dieuf)
- спасибо (mammur)
- спасибо (chokrane mukataze)
- спасибо (lenki)