The anticipated odds ratios to decide the choice of a primary binary endpoint

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Deciding the primary endpoint in a Randomized Clinical Trial

Clinical trial

Evaluating the applicability and comparing the effectiveness of a new intervention against the standard of care.

Protocol:

- formalizes the medical question
- describes the clinical outcomes of greatest interest
- specifies the design and organization of the trial

Assessment of the treatment effect

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

Deciding the primary endpoint in a Randomized Clinical Trial

Reporting more than one efficacy endpoints: Coronary artery disease (TAXUS-V[1])

Placlitaxel-eluting stent (Intervention) versus Bare metal stents (Control)

Primary Endpoint
Relevant Endpoint $\varepsilon_1 \longrightarrow$ **Target-vessel revascularization**
Secondary Endpoint $\varepsilon_2 \longrightarrow$ **Death or myocardial infarction**

[1] 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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Relevant Endpoint $\varepsilon_1 \longrightarrow$ **Target-vessel revascularization**
Secondary Endpoint $\varepsilon_2 \longrightarrow$ **Death or myocardial infarction**
Composite Endpoint $\varepsilon_* = \varepsilon_1 \cup \varepsilon_2 \longrightarrow$ **Major adverse cardiac events**

Composite Endpoint

Combination of several responses into a unique variable.

Advantages:

- More information
- Power might be increased

Disadvantages:

- Challenging interpretation of results
- Power might be reduced

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Outline

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Deciding the primary endpoint in a Randomized Clinical Trial

- Control Group = 0
- Treatment Group = 1

Primary Endpoint	**Binary Response**	**Probabilities**	**Odds**	**Odds Ratio**
Relevant ε_1	X_1	$(p_1^{(0)}, p_1^{(1)})$	$O_1^{(0)} = \frac{p_1^{(0)}}{1-p_1^{(0)}}$	OR_1
Additional ε_2	X_2	$(p_2^{(0)}, p_2^{(1)})$	$O_2^{(0)} = \frac{p_2^{(0)}}{1-p_2^{(0)}}$	OR_2
Composite ε_*	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if } X_1 + X_2 = 0 \end{cases}$	$(p_*^{(0)}, p_*^{(1)})$	$O_*^{(0)} = \frac{p_*^{(0)}}{1-p_*^{(0)}}$	OR_*

Composite Binary Endpoint from its margins

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Probability of ε_* (Bahadur's Theorem [2]):

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

Bounds for Pearson's correlation [3]:

$$\rho^{(i)} \quad \in \quad [\, m(p_1^{(i)}, p_2^{(i)}),\ M(p_1^{(i)}, p_2^{(i)}) \,] \ \subseteq [-1, 1]$$

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

[3] Sozu T., Sugimoto T. and Hamasaki T. (2010). Sample size determination in clinical trials with multiple co-primary binary endpoints. *Stat Med*. **29(21)**, 2169–79.

Composite Binary Endpoint from its margins

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Odds Ratio of ε_*:

$$\mathrm{OR}_* = \frac{\left((1+\mathrm{OR}_1 O_1^{(0)})(1+\mathrm{OR}_2 O_2^{(0)}) - 1 - \rho^{(1)}\sqrt{\mathrm{OR}_1 \mathrm{OR}_2 O_1^{(0)} O_2^{(0)}}\right)}{\left((1+O_1^{(0)})(1+O_2^{(0)}) - 1 - \rho^{(0)}\sqrt{O_1^{(0)} O_2^{(0)}}\right)} \cdot \frac{1+\rho^{(0)}\sqrt{O_1^{(0)} O_2^{(0)}}}{1+\rho^{(1)}\sqrt{\mathrm{OR}_1 \mathrm{OR}_2 O_1^{(0)} O_2^{(0)}}}$$

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Relationship between treatment effects:

$$\mathrm{OR}_1 < 1,\ \mathrm{OR}_2 < 1,\ \rho^{(0)} = \rho^{(1)} = 0 \quad \Rightarrow \quad \mathrm{OR}_* \in [\min(\mathrm{OR}_1, \mathrm{OR}_2),\ \max(\mathrm{OR}_1, \mathrm{OR}_2)]$$

$$\mathrm{OR}_1 = 1,\ \mathrm{OR}_2 = 1,\ \rho^{(0)} = \rho^{(1)} \quad \Rightarrow \quad \mathrm{OR}_* = 1$$

Treatment effects and non-equivalence between hypotheses

Relationship between treatment effects:

$$\mathrm{OR}_1 = 1,\ \mathrm{OR}_2 = 1,\ \rho^{(0)} = \rho^{(1)} \quad \Rightarrow \quad \mathrm{OR}_* = 1$$
$$\mathrm{OR}_1 = 1,\ \mathrm{OR}_2 = 1,\ \rho^{(0)} = \rho^{(1)} \quad \not\Leftarrow \quad \mathrm{OR}_* = 1$$

Primary relevant endpoint ε_1:	Primary composite endpoint ε_*:
$\mathcal{H}_1 : \begin{cases} H_0 : & \log(\mathrm{OR}_1) = 0 \\ H_1 : & \log(\mathrm{OR}_1) < 0 \end{cases}$	$\mathcal{H}_* : \begin{cases} H_0 : & \log(\mathrm{OR}_*) = 0 \\ H_1 : & \log(\mathrm{OR}_*) < 0 \end{cases}$

[4] Gómez G, Lagakos SW. (2013). Statistical considerations when using a composite endpoint for comparing treatment groups. *Stat Med*. Jul 1; 719–38.

[5] Bofill M, Gómez G (2017). Selection of composite binary endpoints in clinical trials.

Treatment effects and non-equivalence between hypotheses

Relationship between treatment effects:

$$\begin{aligned} \mathrm{OR}_1 = 1,\ \mathrm{OR}_2 = 1,\ \rho^{(0)} = \rho^{(1)} \quad &\Rightarrow \quad \mathrm{OR}_* = 1 \\ \mathrm{OR}_1 = 1,\ \mathrm{OR}_2 = 1,\ \rho^{(0)} = \rho^{(1)} \quad &\not\Leftarrow \quad \mathrm{OR}_* = 1 \end{aligned}$$

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Asymptotic Relative Efficiency (ARE) method

The choice between a composite or one of its components as primary endpoint:

- Time-to-event endpoints: Gómez-Lagakos[4].
- Binary endpoints: Bofill-Gómez[5].

[4] Gómez G, Lagakos SW. (2013). Statistical considerations when using a composite endpoint for comparing treatment groups. *Stat Med*. Jul 1; 719–38.

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Outline

Pitman's Asymptotic Relative Efficiency

$$H_0: \quad \log(\mathrm{OR}) = 0$$
$$H_{1,n}: \quad \log(\mathrm{OR})_n = \frac{v}{\sqrt{n}}$$

$$\sqrt{n}\log(\mathrm{OR})_n \longrightarrow v \text{ as } n \to +\infty, \quad v < 0$$

Quantifying the efficiency of $T_{1,n}$, $T_{2,n}$ to attain power $1-\beta$ at level α

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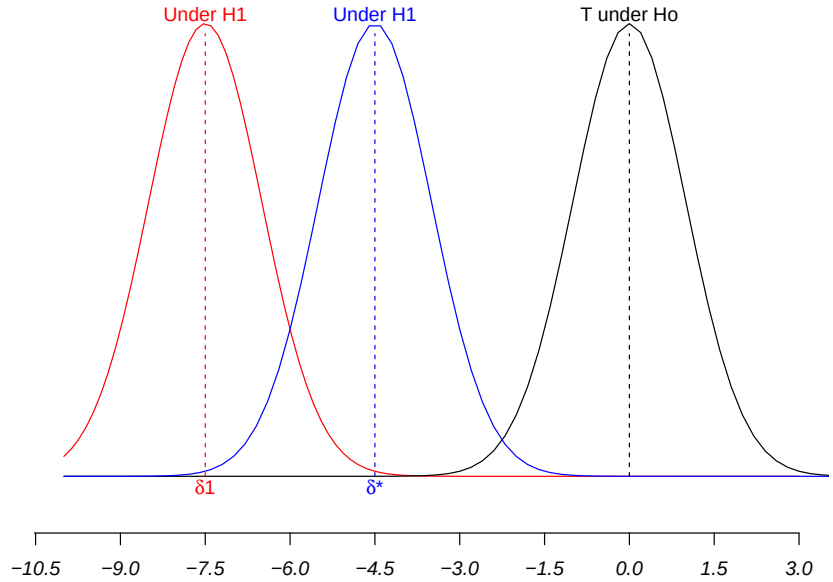
$$\sqrt{n}\log(\mathrm{OR})_n \longrightarrow v \text{ as } n \to +\infty, \quad v < 0$$

$$T_{1,n} \to N(0,1), \quad T_{2,n} \to N(0,1), \quad \text{under } H_0$$
$$T_{1,n} \to N(\delta_1,1), \quad T_{2,n} \to N(\delta_2,1), \quad \text{under } H_{1,n}$$



Asymptotic Relative Efficiency:

$$A(T_{1,n}, T_{2,n}) = \left(\frac{\delta_1}{\delta_2}\right)^2$$

Sample Size:

$$A(T_{1,n}, T_{2,n}) = \lim_{n\to+\infty} \frac{n_2(\alpha,\ \beta,\ \log(\mathrm{OR})_n)}{n_1(\alpha,\ \beta,\ \log(\mathrm{OR})_n)}$$

ARE method for Binary Endpoints

Primary relevant endpoint ε_1:

$$\mathcal{H}_1: \begin{cases} H_0: & \log(\mathrm{OR}_1) = 0 \\ H_{1,n}: & \log(\mathrm{OR}_1)_n = \frac{v_1}{\sqrt{n}} \end{cases}$$

Primary composite endpoint ε_*:

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Score Statistic: $T_{1,n}$

- Under H_0: $T_{1,n} \longrightarrow N(0,1)$
- Under $H_{1,1}$:
  $T_{1,n} \longrightarrow N\left(v_1\sqrt{p_1^{(0)}q_1^{(0)}\pi(1-\pi)},\ 1\right)$

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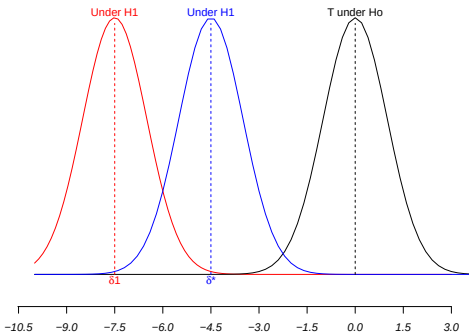

Asymptotic Relative Efficiency:

$$\mathrm{ARE}(T_{*,n}, T_{1,n}\,;\, p_1^{(0)}, p_2^{(0)}, \rho^{(0)}, \rho^{(1)}, v_1, v_*) = \frac{v_*^2}{v_1^2} \cdot \frac{p_*^{(0)} q_*^{(0)}}{p_1^{(0)} q_1^{(0)}}$$

ARE method for fixed alternatives

$$\text{ARE}(T_{*,n}, T_{1,n}) \quad = \quad \frac{v_*^2}{v_1^2} \cdot \frac{p_*^{(0)} q_*^{(0)}}{p_1^{(0)} q_1^{(0)}}$$

- Limiting treatments
- Applicability for fixed alternatives

ARE method for fixed alternatives

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- Limiting treatments
- Applicability for fixed alternatives

Fixed alternatives approach:

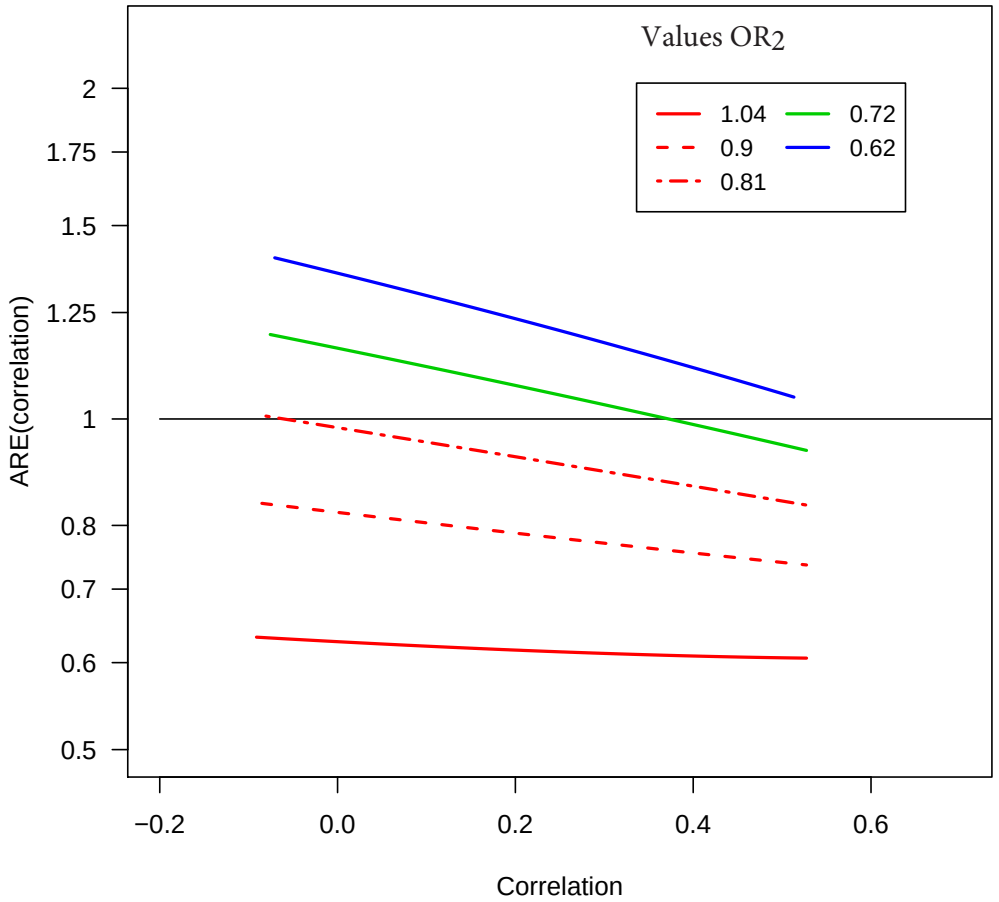
$$\begin{aligned} \sqrt{n}\log(\text{OR}_1) &\cong v_1 \\ \sqrt{n}\log(\text{OR}_*) &\cong v_* \end{aligned}$$

$$are(\text{OR}_1, \text{OR}_2, p_1^{(0)}, p_2^{(0)}, \rho^{(0)}, \rho^{(1)}) \quad = \quad \frac{(\log(\text{OR}_*))^2}{(\log(\text{OR}_1))^2} \cdot \frac{p_*^{(0)} q_*^{(0)}}{p_1^{(0)} q_1^{(0)}}$$

Criterion

- $are > 1 \Longrightarrow$ composite endpoint ε_* as primary endpoint.
- $are \leq 1 \Longrightarrow$ relevant endpoint ε_1 as primary endpoint.

TAXUS-V:
Target-vessel revascularization versus Major adverse cardiac events



Primary endpoints:

- ε_*: **Composite Endpoint** Major adverse cardiac events
- ε_1: **Relevant Endpoint** Target-vessel revascularization
- ε_2: Death or Myocardial infarction

Parameters:

- $p_1^{(0)} = 0.173$;
- $p_2^{(0)} = 0.055$;
- $\mathrm{OR}_1 = 0.67$;
- $\mathrm{OR}_2 = 1.04, 0.90, 0.81, 0.72, 0.62$;
- Assuming $\rho = \rho^{(0)} = \rho^{(1)}$, then: $\rho \in (-0.09, 0.53)$

The composite endpoint becomes more useful when OR_2 shows a larger effect.

Outline

Statistical efficiency guidelines

Settings used for the guidelines:

- $0 < p_1^{(0)},\ p_2^{(0)} < 0.1$
- $0.5 \leq \mathrm{OR}_1,\ \mathrm{OR}_2 < 1$
- $0 \leq \rho < 1$

Total Number of Scenarios: 315348

Criterion:

- $are > 1 \Longrightarrow$ composite endpoint ε_* as primary endpoint.
- $are \leq 1 \Longrightarrow$ relevant endpoint ε_1 as primary endpoint.

$\Longrightarrow$ **percentage of cases** on which the composite is preferred over the relevant endpoint.

Statistical efficiency guidelines

Recommendations in terms of the anticipated effects

- Large: OR between 0.5 and 0.7
- Medium: OR between 0.7 and 0.9
- Low: OR between 0.9 and 1

	Large OR_2	Medium OR_2	Low OR_2
Large OR_1	**CE** 91%	**RE** 23%	**RE** 0%
Medium OR_1	**CE** 100%	**CE** 84%	**RE** 7%
Low OR_1	**CE** 100%	**CE** 100%	**CE** 69%

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	Large OR_2	Medium OR_2	Low OR_2
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Low OR_1	**CE** 100%	**CE** 100%	**CE** 69%

Recommendations in terms of the effects and correlation

- Weak: $0 < \rho < 0.3$
- Medium-weak: $0.3 \leq \rho < 0.6$
- Medium-strong: $0.6 \leq \rho < 0.8$
- Strong: $0.8 \leq \rho < 1$

Treatment effect \ Correlation	Weak	Medium-weak	Medium-strong	Strong
Large effect ε_2	**CE** 99,72%	**CE** 97,41%	**CE** 92,87%	**CE** 84,97%
Medium effect ε_2	**CE** 74,96%	**CE** 65,97%	**CE/RE** 58,23%	**CE/RE** 56,96%
Low effect ε_2	**RE** 23,61%	**RE** 21,39%	**RE** 20,99%	**RE** 28,16%
Large effect ε_1	**CE/RE** 49,80%	**CE/RE** 42,29%	**RE** 35,72%	**RE** 38,00%
Medium effect ε_1	**CE** 73,47%	**CE** 68,72%	**CE** 63,04%	**CE/RE** 57,78%
Low effect ε_1	**CE** 92,16%	**CE** 91,05%	**CE** 89,87%	**CE** 86,61%

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Final remarks

- ARE method: Convenient tool to provide an informed selection between a binary composite endpoint or one of its components as primary endpoint.
- Use of Composite Endpoints has to be justified from a clinical point of view.

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Future Research

- Sample Size for Composite Binary Endpoints.
- The ARE method as ratio of sample sizes.
- Extension of the ARE method to other comparisons (Composite versus Multiple Primary Endpoints).
- Implementation in the web platform and Shiny application *CompARE*.


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