The efficient choice of a primary binary endpoint for sample size assessment

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Deciding the primary endpoint in a Randomized Clinical Trial

Assessment of the treatment effect

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

- The choice of the primary endpoint is an important issue when designing a clinical trial.

Composite Endpoint

Combination of several responses into a unique variable.

Advantages:

- More information about the disease
- Power might be increased

Disadvantages:

- Challenging interpretation of results
- Power might be reduced

Aims of the talk

Binary Composite Endpoints

Composite endpoint in terms of its binary components

ARE method

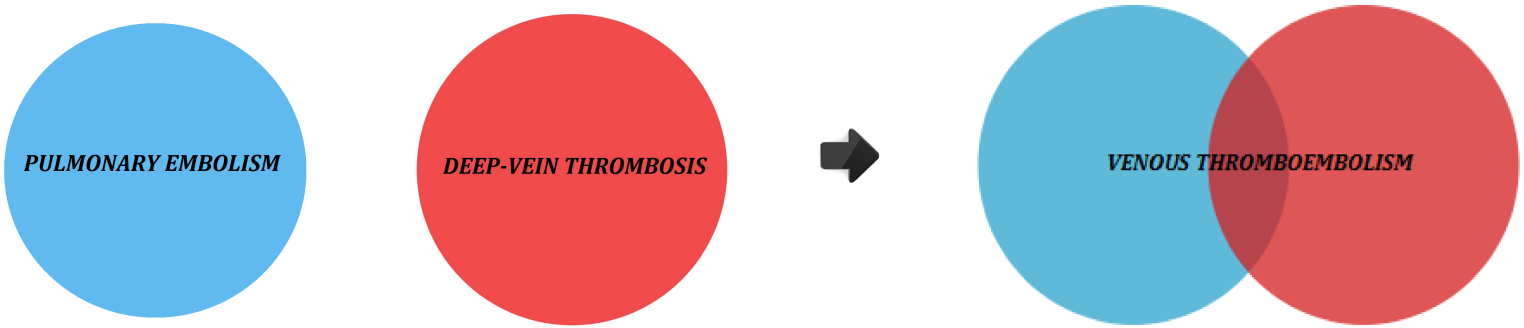
Method based on the Asymptotic Relative Efficiency (ARE) discerning between a binary composite endpoint or one of its components as primary endpoint of the trial.

ARE method and Sample Size

Relationship between the ARE method and the sample size

Venous Thromboembolism Study[1]

Primary Endpoint	Binary Response	Probabilities
Deep-vein thrombosis ε_1	X_1	p_1
Pulmonary embolism ε_2	X_2	p_2
Venous thromboembolism ε_*	$X_* = \begin{cases} 1, \text{ if } X_1 + X_2 \geq 1 \\ 0, \text{ if else } X_1 + X_2 = 0 \end{cases}$	p_*



[1] Bauer KA, et al. (2001). *Fondaparinux compared with Enoxaparin for the prevention of venous thromboembolism after elective major knee surgery*. N Engl J Med.

Binary Endpoints

Consider two binary endpoints:

$$\begin{aligned} X_1 &\sim Ber(p_1) \\ X_2 &\sim Ber(p_2) \\ \rho &= Corr(X_1, X_2) \end{aligned}$$

where: $p_i = 1 - q_i = P(X_i = 1)$

Bahadur's Theorem[2]:

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

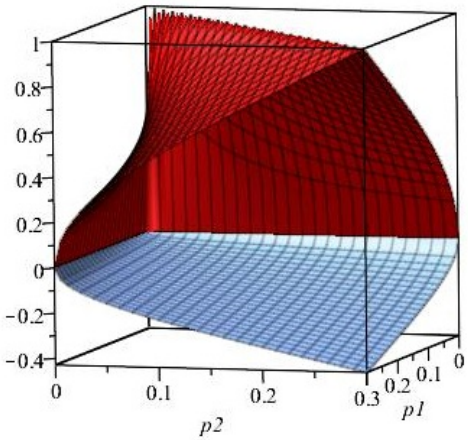


Figure: $p_1, p_2 \in (0, 0.3)$

Correlation's bounds:

$$\rho \in [\, m(p_1, p_2),\ M(p_1, p_2)\,] \subseteq [-1, 1]$$

[2] Bahadur RR. (1961) *A representation of the joint distribution of responses to n dichotomous items*. Stanford University Press.

Venous Thromboembolism Study: Fondaparinux versus Enoxaparin

Primary Endpoint	**Probabilities**	**Odds Ratio**
Deep-vein thrombosis ε_1	$(p_1^{(0)}, p_1^{(1)})$	OR_1
Pulmonary embolism ε_2	$(p_2^{(0)}, p_2^{(1)})$	OR_2
Venous Thromboembolism ε_*	$(p_*^{(0)}, p_*^{(1)})$	OR_*

Venous Thromboembolism Study: Fondaparinux versus Enoxaparin

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Probability of ε_*:

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

Odds Ratio of ε_*:

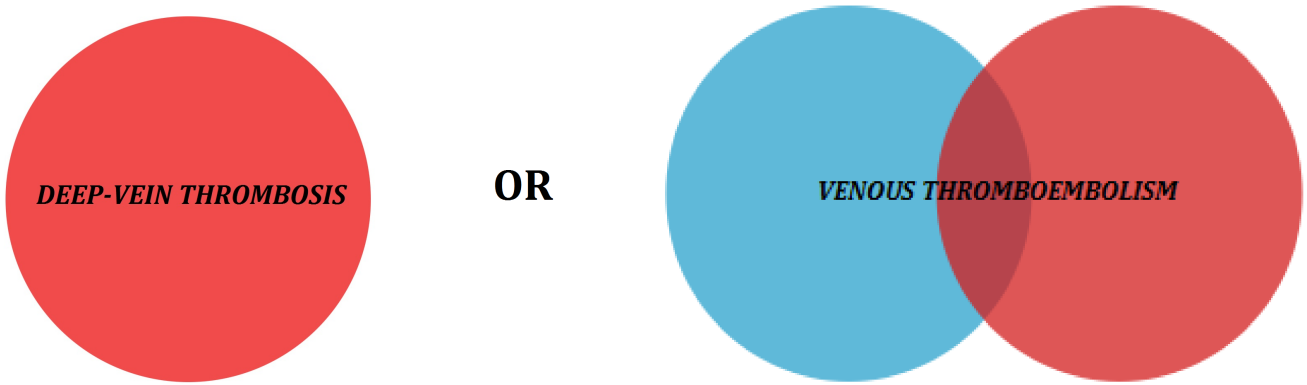
$$\mathrm{OR}_* = \frac{\left((1+\mathrm{OR}_1 O_1^{(0)})(1+\mathrm{OR}_2 O_2^{(0)}) - 1 - \rho^{(1)} \sqrt{\mathrm{OR}_1 \mathrm{OR}_2 O_1^{(0)} O_2^{(0)}}\right)}{\left((1+O_1^{(0)})(1+O_2^{(0)}) - 1 - \rho^{(0)} \sqrt{O_1^{(0)} O_2^{(0)}}\right)} \frac{1+\rho^{(0)} \sqrt{O_1^{(0)} O_2^{(0)}}}{1+\rho^{(1)}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

where: $O_1^{(0)} = p_1^{(0)}/q_1^{(0)}$ and $O_2^{(0)} = p_2^{(0)}/q_2^{(0)}$.

Choice of the primary endpoint

Treatment effects

- If $OR_1 = 1, OR_2 = 1$ and $\rho^{(0)} = \rho^{(1)}$, then $OR_* = 1$.
- If $p_1^{(0)} = p_1^{(1)}, p_2^{(0)} = p_2^{(1)}$ and $\rho^{(0)} = \rho^{(1)}$, then $p_*^{(0)} = p_*^{(1)}$.



Choice of the primary endpoint

Treatment effects

- If $\mathrm{OR}_1 = 1, \mathrm{OR}_2 = 1$ and $\rho^{(0)} = \rho^{(1)}$, then $\mathrm{OR}_* = 1$.
- If $p_1^{(0)} = p_1^{(1)}, p_2^{(0)} = p_2^{(1)}$ and $\rho^{(0)} = \rho^{(1)}$, then $p_*^{(0)} = p_*^{(1)}$.

Primary Endpoint ε_1: Deep-vein thrombosis

$$\mathcal{H}_1 : \begin{cases} H_0 : & \log(\mathrm{OR}_1) = 0 \\ H_1 : & \log(\mathrm{OR}_1) < 0 \end{cases}$$

Composite Endpoint ε_*: Venous Thromboembolism

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

Pitman's Asymptotic Relative Efficiency

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

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

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

Pitman's Asymptotic Relative Efficiency

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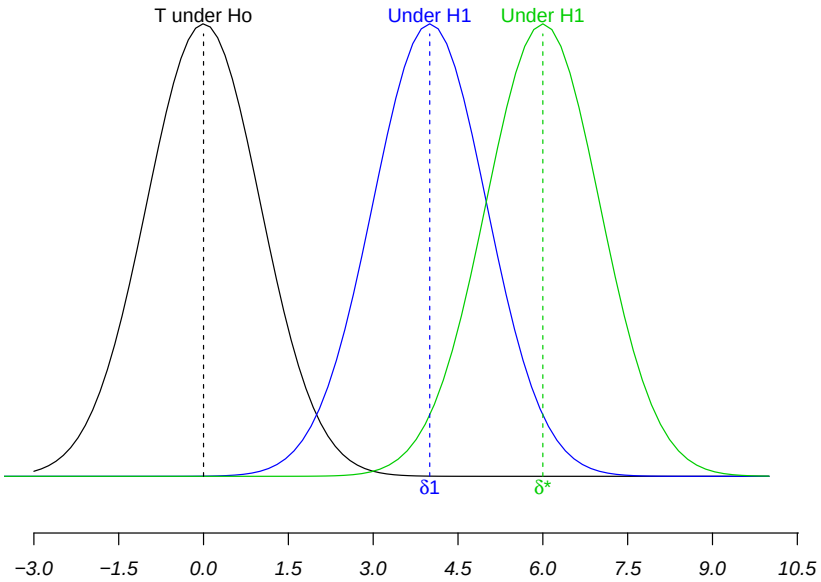
Quantifying the efficiency of $T_{1,n}$, $T_{2,n}$ to attain power $1-\beta$ at level α

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

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



Asymptotic Relative Efficiency:

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

Sample Size:

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

Choice of the primary endpoint: ARE method

ARE method

The choice between a composite or one of its components as primary endpoint (Gómez-Lagakos[3])

Primary Endpoint ε_1: Deep-vein thrombosis

$$\mathcal{H}_1: \begin{cases} H_0: & \log(\mathrm{OR}_1) = 0 \\ H_1: & \log(\mathrm{OR}_1) < 0 \end{cases}$$

Composite Endpoint ε_*: Venous Thromboembolism

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

[3] Gómez G, Lagakos SW. (2013). *Statistical considerations when using a composite endpoint for comparing treatment groups*. Stat Med.

ARE method for Binary Endpoints

Deep-vein thrombosis

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

Score Statistic: $T_{1,n}$

Under H_0:
$T_{1,n} \longrightarrow N(0,1)$

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

Venous Thromboembolism

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

ARE method for fixed alternatives

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

- Limiting treatments
- Applicability for fixed alternatives

ARE method for fixed alternatives

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

- Limiting treatments
- Applicability for fixed alternatives

Fixed alternatives approach

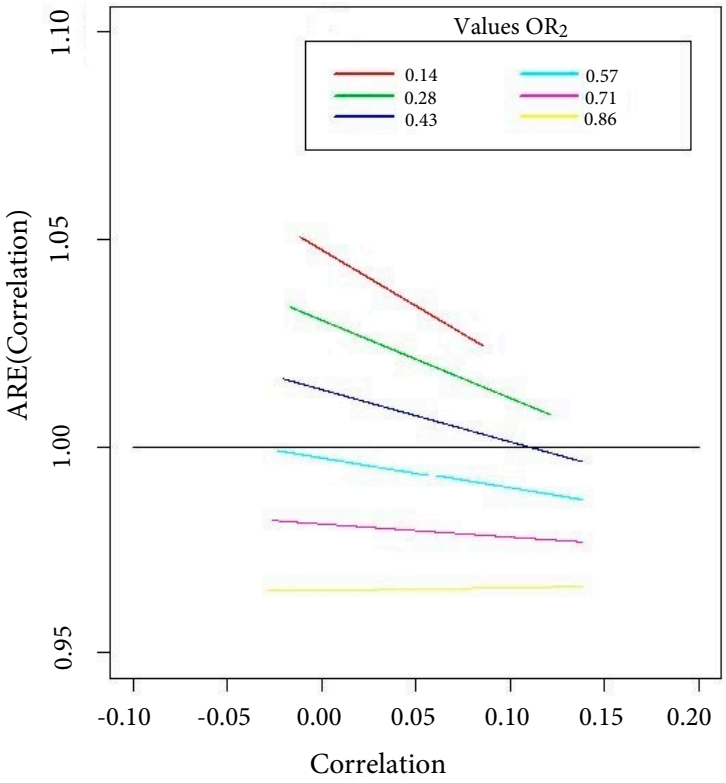
$$\begin{aligned} \sqrt{n}\log(\text{OR}_1) &\cong v_1 \\ \sqrt{n}\log(\text{OR}_*) &\cong v_* \end{aligned}$$

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

Criterion

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

Venous Thromboembolism Study



- Primary endpoints:
  - ε_*: Venous thromboembolism
  - ε_1: Deep-vein thrombosis
  - ε_2: Pulmonary embolism
- Parameters:
  - $p_1^{(0)} = 0.27$;
  - $p_1^{(1)} = 0.12$;
  - $p_2^{(0)} = 0.007$;
  - $p_2^{(1)} \in 0.001, 0.002, 0.003, 0.004, 0.005, 0.006$;
  - Assuming $\rho^{(0)} = \rho^{(1)}$, then: $\rho \in (-0.03, 0.14)$

- *are* decreases when OR_2 grows
- *are* decreases when the correlation increases
- *are* values are always in the vicinity of one

ARE method and Sample Sizes

$$are(\mathrm{OR}_1, \mathrm{OR}_2, p_1^{(0)}, p_2^{(0)}, \rho) \quad \stackrel{?}{=} \quad \frac{n_1(\alpha, \beta, \mathrm{OR}_1)}{n_*(\alpha, \beta, \mathrm{OR}_*)}$$

Scenarios

- Similar treatment effect of the components of a composite
- Small treatment effects

Other measures

- Relative Efficiency
- Bahadur's Asymptotic Relative Efficiency

Future Research

- The ARE method as ratio of sample sizes
- Extension of the ARE method to other comparisons (Composite versus Multiple Co-Primary Endpoints)
- Extension of the ARE method for equivalent tests and observational cohort studies.
- Implementation in the web platform CompARE.
- Comparison of two nonequivalent sets of hypotheses.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Баярлалаа
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