

CompARE: a web app to study Composite Endpoints

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BGSMath
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Primary Composite Endpoints

Primary endpoint

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

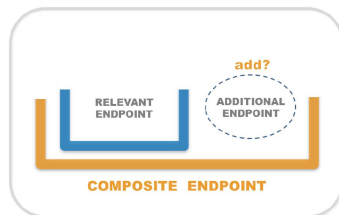
More than one relevant outcome to measure the efficacy of an intervention

- **MACE** in cardiovascular trials: Death (ε_1), MI (ε_2) and Rehospitalization (ε_3)
- **PFS** in oncology trials: Death (D, ε_1) and Disease Progression (P, ε_2)

Composite Events ε_*

Combination of several outcomes, $\varepsilon_1, \varepsilon_2, \dots$
into a single composite endpoint

$$\varepsilon_* = \varepsilon_1 \cup \varepsilon_2$$



Our work on CE has motivated the web platform CompARE

Research Article

Statistics
in Medicine

Statistical considerations when using a composite endpoint for comparing treatment groups

Guadalupe Gómez^{a,†} and Stephen W. Lagakos^{b,‡}

Time to event endpoint

Primer on Statistical Interpretation or Methods

Informed Choice of Composite End Points in Cardiovascular Trials

Guadalupe Gómez, PhD; Moisés Gómez-Mateu, MSc; Urania Dafni, ScD

JOURNAL OF BIOPHARMACEUTICAL STATISTICS
<https://onlinelibrary.wiley.com/doi/10.1002/jbbs.12113>



Selecting the primary endpoint in a randomized clinical trial: The ARE method

Oleguer Plana-Ripoll¹ and Guadalupe Gómez²

SORT 38 (1) January-June 2014, 73-88

The asymptotic relative efficiency and the ratio of sample sizes when testing two different null hypotheses

Guadalupe Gómez^{1,2} and Moisés Gómez-Mateu¹

Selection of the primary endpoint in an observational cohort study

Guadalupe Gómez,¹ Oleguer Plana-Ripoll,² Urania Dafni^{3,4}

Binary endpoint

RESEARCH PAPER

Biometrical Journal

Selection of composite binary endpoints in clinical trials

Marta Bofill Roig¹ | Guadalupe Gómez Melis²

RESEARCH ARTICLE

WILEY Statistics
in Medicine

A new approach for sizing trials with composite binary endpoints using anticipated marginal values and accounting for the correlation between components

Marta Bofill Roig¹ | Guadalupe Gómez Melis²

ARE: ASSESSING RELATIVE EFFICIENCY BETWEEN USING \mathcal{E}_1 VERSUS $\mathcal{E}^* = \mathcal{E}_1 \cup \mathcal{E}_2$

- Logrank for T_1 : time to \mathcal{E}_1
- Logrank for T_* : time to \mathcal{E}_*

$$Z \sim N(\mu_1, 1)$$

$$Z_* \sim N(\mu_*, 1)$$

$$\text{ARE}(Z_*, Z) = \left(\frac{\mu_*}{\mu_1}\right)^2 = \frac{\left(\int_0^1 \log\left\{\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right\} f_*^{(0)}(t) dt\right)^2}{(\log \text{HR}_1)^2 p_*^{(0)} p_1^{(0)}} = \frac{(\text{ALHR})^2}{(\log \text{HR}_1)^2} \cdot \frac{p_*^{(0)}}{p_1^{(0)}}$$

- **ARE depends on:** 1) T_1 via p_1 and HR_1 , 2) T_2 via p_2 and HR_2 , 3) (T_1, T_2) via a Copula and Spearman's rank correlation, ρ , between T_1 and T_2 (assumed equal for both groups)

Criterion for Decision

$\text{ARE}(Z_*, Z) > 1 \Rightarrow T_*$ **more efficient than** $T_1 \Rightarrow$ Use composite endpoint

Pitman's Interpretation of ARE

n_1 and n_* : sample sizes required for Z and Z_* to have power $1 - \beta$ at level α . Given $0 < \alpha < 1 - \beta < 1$,

$$\text{ARE} = \frac{e_1}{e_*} \frac{p_*^{(0)}}{p_1^{(0)}} = \frac{n_1}{n_*} \frac{1 + \frac{p_*^{(1)}}{p_*^{(0)}}}{1 + \frac{p_1^{(1)}}{p_1^{(0)}}}$$

CompARE
<http://cinna.upc.edu/compare/>

What is CompARE?

CompARE is a web-platform inspired to provide help on issues relating to trials with composite endpoints. **CompARE** may be used as a tool for calculating the elements needed in the planning phase of clinical trials involving composite endpoints. With its user-friendly interface, CompARE allows to input the main parameters included in the trial -such as the treatment effect on the components of the composite endpoint, and its frequencies of occurrence- and helps provide power and sample size calculations among others.

Features



Effect Size

Studying the treatment effect for the composite endpoint.

Time to event Binary



Sample Size

Computing the number of patients under different scenarios

Time to event Binary



Endpoint Selection

Identifying the best endpoint combination for the design

Time to event Binary



Association

Assessing the degree of association between components

Binary

Apps

CompARE is split into two apps for time-to-event and binary endpoints, respectively. They are implemented with the Shiny R package

[GO TO TIME-TO-EVENT SHINY](#)[GO TO BINARY SHINY](#)

ZODIAC Trial (1)

- **Population:** patients with advanced non-small-cell lung cancer
- **Experimental intervention (1):** vandetanib plus docetaxel
- **Reference intervention (0):** placebo plus docetaxel
- **Endpoint (ϵ_1):** Time (T_1) from randomization (R) to D (*Death*)
- **Endpoint (ϵ_2):** Time (T_2) from R to P (*Disease progression*)
- **Composite endpoint (ϵ_*):** Time (T_*) from R to PFS (*Death or Progression*)
- Double-blind, randomised, phase 3 trial

1. Endpoint selection

How to choose between the composite endpoint and one of its components

2. Effect size

How to specify the expected **treatment effect?**
Behavior of the **Hazard ratio** $HR_*(t)$ for the CE

TACTICS Trial to illustrate Composite Binary Endpoints

3. Sample size

Required sample size for the composite endpoint

(1) Herbst RS et al. (2010). The Lancet Oncology

Zodiac Trial: Input Parameters and Assumptions

Notation

Endpoint 1: $\varepsilon_1 = \text{Death}$, Endpoint 2: $\varepsilon_2 = \text{Disease Progression}$, Endpoint CE: $\varepsilon_* = \text{PFS}$

Endpoint 1		Relationship between endpoints	
Probability	Hazard ratio	Correlation	Type
<input type="text" value="0.59"/>	<input type="text" value="0.91"/>	<input type="text" value="0.5"/>	<input type="text" value="Spearman's rho"/>
Risk over time	<input checked="" type="checkbox"/> Death	Copula	
<input type="text" value="Constant"/>		<input type="text" value="Frank"/>	
Endpoint 2		Alpha and Power	
Probability	Hazard ratio	Significance level	Power
<input type="text" value="0.74"/>	<input type="text" value="0.77"/>	<input type="text" value="0.05"/>	<input type="text" value="0.8"/>
Risk over time	<input type="checkbox"/> Death	Formula	
<input type="text" value="Constant"/>		<input type="text" value="Freedman"/>	

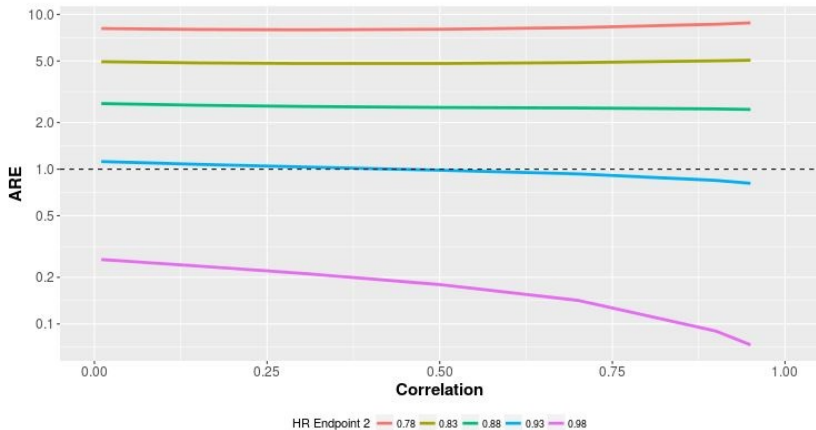
Assumptions

- HR_1 and HR_2 constant over time
- Weibull distributions for T_1 and T_2 with common shape parameter in both arms
- Copula to bind T_1 and T_2
- Same correlation (ρ) between T_1 and T_2 in both arms

ZODIAC Trial: Should we use time to Death (D) or PFS?

Study of the efficiency of PFS (CE) versus D as a function of the correlation (ρ) between D and Progression (P) and for 5 different HR_2 for Progression

$$HR_1 = 0.91 \quad p_1 = 0.59 \quad p_2 = 0.74$$



ZODIAC Trial: If we use PFS, how does its effect size behave?

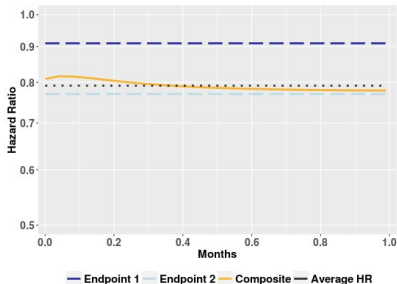
Hazard Ratio for PFS, $HR_*(t) = \frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}$, depends on:

$(p_1, p_2, HR_1, HR_2, \rho)$, marginal hazard behaviours (β_1, β_2) , copula to bind T_1 and T_2 and whether death is included (cause specific hazards used instead)

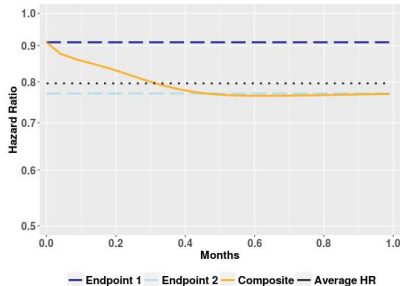
- $HR_1 = 0.91$
- $HR_2 = 0.77$
- $p_1 = 0.59$
- $p_2 = 0.74$

- $\rho = 0.5$
- $\beta_1 = 1$
- $\beta_2 = ?$

Constant hazard for P ($\beta_2 = 1$)



Increasing hazard for P ($\beta_2 = 2$)



ZODIAC Trial to illustrate Time-to-event endpoints (T2E)

1. Endpoint selection

How to choose between the composite endpoint and one of its components

2. Effect size

How to specify the expected **treatment effect**?
Behavior of the **Hazard ratio** $HR_*(t)$ for the CE

TACTICS Trial (2)

- **Population:** patients with unstable angina or non-Q-wave AMI
- **Invasive intervention (1):** cardiac catheterization and revascularization with angioplasty or bypass surgery if feasible
- **Conservative intervention (0):** catheterization only for recurrent pain at rest or provokable ischemia
- **Endpoint (ϵ_1):** Death or MI
- **Endpoint (ϵ_2):** Rehospitalization
- **Composite endpoint (ϵ_*):** MACE

3. Sample size

Required sample size for the composite endpoint

(2) Cannon, CP, et al. (1998). *American Journal of Clinical Oncology*

TACTICS-TIMI 18 Trial: Input Parameters and Assumptions

Notation

Endpoint 1: Death or MI, Endpoint 2: Rehospitalization, CE: MACE

The screenshot displays a web-based interface for configuring trial parameters. It is divided into three main sections: ENDPOINTS, ASSOCIATION, and ALPHA AND POWER. The ENDPOINTS section is further divided into Composite Endpoint, Endpoint 1, and Endpoint 2. Each endpoint configuration includes a dropdown for 'Effect measure' (set to 'Risk difference'), a 'Probability under control group' dropdown (set to 'Point value'), and a slider for 'Anticipated value' (ranging from 0.01 to 0.5). Endpoint 1 also includes a 'Risk Difference' slider (ranging from -0.2 to 0.001). The ASSOCIATION section includes a 'Relationship between components' slider (ranging from 0 to 1). The ALPHA AND POWER section includes 'Significance level' (0.05) and 'Power' (0.8) input fields.

ENDPOINTS | **ASSOCIATION** | **ALPHA AND POWER**

Composite Endpoint:
Effect measure: Risk difference

Endpoint 1:
Probability under control group: Point value
Anticipated value: 0.01 | 0.095 | 0.5
Effect measure: Risk difference
Risk Difference: -0.2 | -0.022 | 0

Endpoint 2:
Probability under control group: Point value
Anticipated value: 0.01 | 0.137 | 0.5
Effect measure: Risk difference
Risk Difference: -0.2 | -0.027 | 0
Relationship between components: 0 | 0.2 | 1

Alpha and Power
Significance level: 0.05 | Power: 0.8

Assumptions

Same correlation (ρ) between components in both arms

Testing problem: Should we adopt the invasive strategy?

$$\mathcal{H}_* : \begin{cases} H_0 : \delta_* = p_*^{(1)} - p_*^{(0)} = 0 \\ H_1 : \delta_* = p_*^{(1)} - p_*^{(0)} < 0 \end{cases}$$

Sample size formula for composite binary endpoints (n)

$$n_*(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho) = 2 \cdot \left(\frac{z_\alpha + z_\beta}{\delta_*} \right)^2 \cdot \left(p_*^{(0)} \cdot (1 - p_*^{(0)}) + (p_*^{(0)} + \delta_*) \cdot (1 - p_*^{(0)} - \delta_*) \right)$$

Anticipating δ_* and $p_*^{(0)}$ is not an easy task!

$$p_*^{(i)} = 1 - q_1^{(i)} q_2^{(i)} - \rho \sqrt{p_1^{(i)} p_2^{(i)} q_1^{(i)} q_2^{(i)}}$$
$$\delta_* = \delta_1 q_2^{(0)} + \delta_2 q_1^{(0)} - \delta_1 \delta_2 + \rho \left(\sqrt{p_1^{(0)} p_2^{(0)} q_1^{(0)} q_2^{(0)}} - \sqrt{(p_1^{(0)} + \delta_1)(p_2^{(0)} + \delta_2)(q_1^{(0)} - \delta_1)(q_2^{(0)} - \delta_2)} \right)$$

Sample Size $n_*(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2, \rho)$ for the TACTICS trial

Endpoint 1:

Probability under control group:
Point value

Anticipated value:
0.095

Effect measure:
Risk Difference

Risk Difference:
-0.022

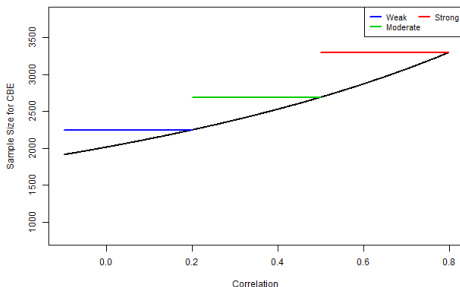
Endpoint 2:

Probability under control group:
Point value

Anticipated value:
0.137

Effect measure:
Risk Difference

Risk Difference:
-0.027



Sample size is highly sensitive to the association:

- $\rho = 0.1 \Rightarrow n = 2125$
- $\rho = 0.3 \Rightarrow n = 2383$
- $\rho = 0.5 \Rightarrow n = 2695$
- $\rho = 0.7 \Rightarrow n = 3080$

Sample Size $n_*(p_1^{(0)}, p_2^{(0)}, \delta_1, \delta_2)$ varying ρ for the TACTICS trial

Endpoint 1:

Probability under control group:
Point value

Anticipated value:
0.095

Effect measure:
Risk Difference

Risk Difference:
-0.022

Endpoint 2:

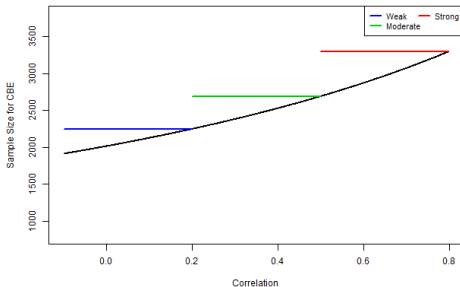
Probability under control group:
Point value

Anticipated value:
0.137

Effect measure:
Risk Difference

Risk Difference:
-0.027

- 1 Define correlation categories: WEAK/MODERATE/STRONG
- 2 Compute their corresponding bounds ρ_{\min} and ρ_{\max}
- 3 Calculate the maximum sample size value in each correlation category

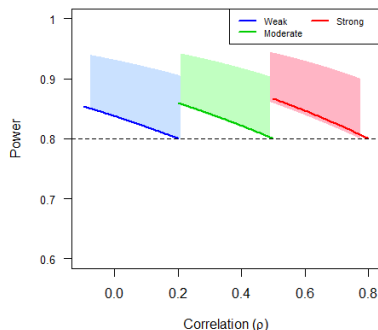
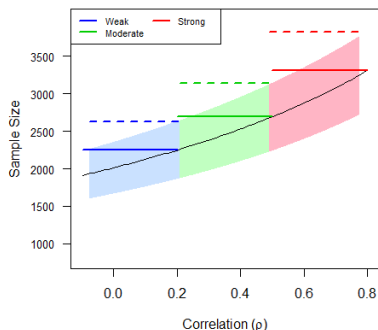


Sample Size and Power for **Intervals** of plausible values for the event rates varying ρ for the TACTICS trial

Intervals of plausible values for the event rates:

$$I_1^{(0)} = [0.078, 0.112] \text{ for the event rate } p_1^{(0)}$$

$$I_2^{(0)} = [0.117, 0.157] \text{ for the event rate } p_2^{(0)}$$



Solid line: Based on point values $p_1^{(0)} = 0.095$, $p_2^{(0)} = 0.137$

Shaded areas: Based on the intervals $I_1 = [0.078, 0.112]$ and $I_2 = [0.117, 0.157]$.

- Binary endpoints
 - Other measures of **association** and their relationships
 - Extension to **Sequential** designs
- Time-to-Event endpoints
 - Flexibility on **Recruitment** times
 - Implementation of Average Hazard Ratio **AHR** (Kalbfleisch and Prentice)
 - Other HR summaries when proportionality of the hazards is violated.
 - Add **simulation** tools to check statistical significance and power

If your study involves several outcomes, you are interested in their union and you need to know:

- Probability of occurrence of their union
- Odds Ratio of the CE

$$OR_* = \frac{\left(\left(1 + \frac{OR_1 p_1^{(0)}}{1-p_1^{(0)}} \right) \left(1 + \frac{OR_2 p_2^{(0)}}{1-p_2^{(0)}} \right) - 1 - \rho \sqrt{\frac{OR_1 OR_2 p_1^{(0)} p_2^{(0)}}{(1-p_1^{(0)})(1-p_2^{(0)})}} \right) \cdot \left(1 + \rho \sqrt{\frac{p_1^{(0)} p_2^{(0)}}{(1-p_1^{(0)})(1-p_2^{(0)})}} \right)}{\left(\left(1 + \frac{p_1^{(0)}}{(1-p_1^{(0)})} \right) \cdot \left(1 + \frac{p_2^{(0)}}{(1-p_2^{(0)})} \right) - 1 - \rho \sqrt{\frac{p_1^{(0)} p_2^{(0)}}{(1-p_1^{(0)})(1-p_2^{(0)})}} \right) \cdot \left(1 + \rho \sqrt{\frac{OR_1 OR_2 p_1^{(0)} p_2^{(0)}}{(1-p_1^{(0)})(1-p_2^{(0)})}} \right)}$$

- Survival and hazard functions for time to the first event
- etc, etc, etc...

DO NOT HESITATE AND USE COMPARE

<http://cinna.upc.edu/compare/>

THANKS A LOT FOR YOUR ATTENTION

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