CompARE: a web app to study Composite Endpoints

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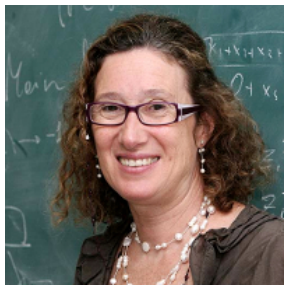

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Primary Composite Endpoints

Primary endpoint

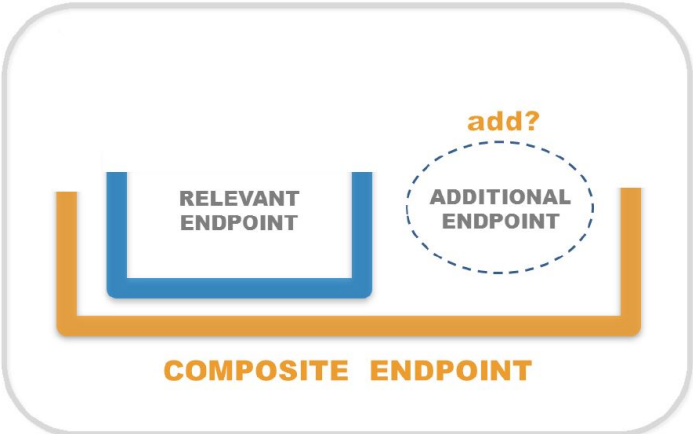
The **primary endpoint** measures the clinical evidence in a clinical trial.

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, ε_1,ε_2,... 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
http://dx.doi.org/10.1080/10543406.2015.1094808

Taylor & Francis
Taylor & Francis Group

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

Oleguer Plana-Ripoll[a] and Guadalupe Gómez[b]

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] and Moisés Gómez-Mateu[1]

Selection of the primary end point 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 Roig | Guadalupe Gómez Melis

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 Roig | Guadalupe Gómez Melis

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 $\mathcal{E}_1$ $\quad Z \sim N(\mu_1, 1)$
- Logrank for T_* : time to $\mathcal{E}_*$ $\quad Z_* \sim N(\mu_*, 1)$

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

- **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

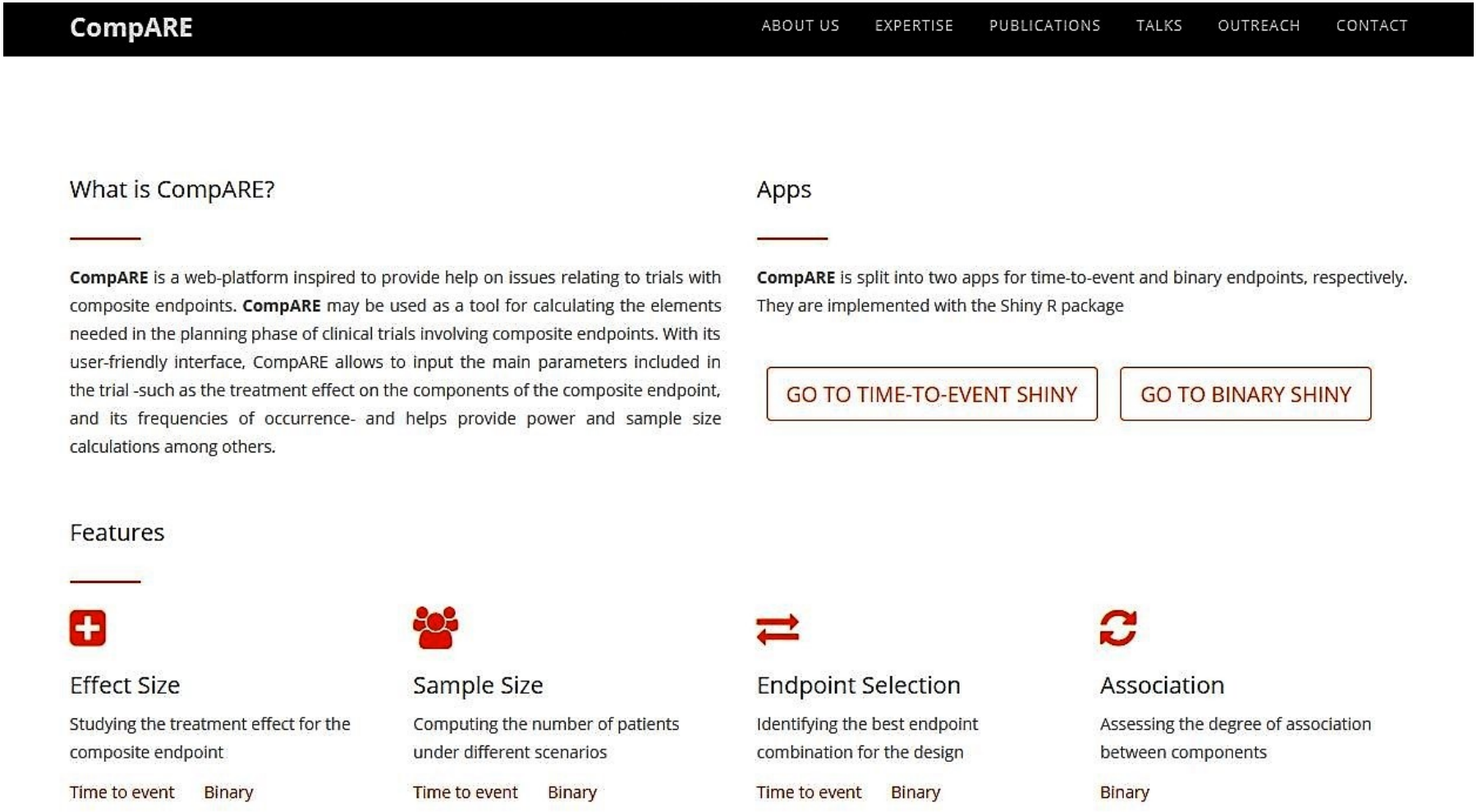
n_1 and n_*: sample sizes required for Z and Z_* to have power $1-\beta$ at level α. Given $0 < \alpha < 1-\beta < 1$,

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

CompARE

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

CompARE Home Page



Use CompARE to solve your CE research questions. Two case studies

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 chose between the composite endpoint and one of its components

2. Effect size

How to specify the expected **treatment effect**? Behavior of the **Hazard ratio** $\mathrm{HR}_*(t)$ for the CE

TACTICS Trial to illustrate Composite Binary Endpoints

3. Sample size

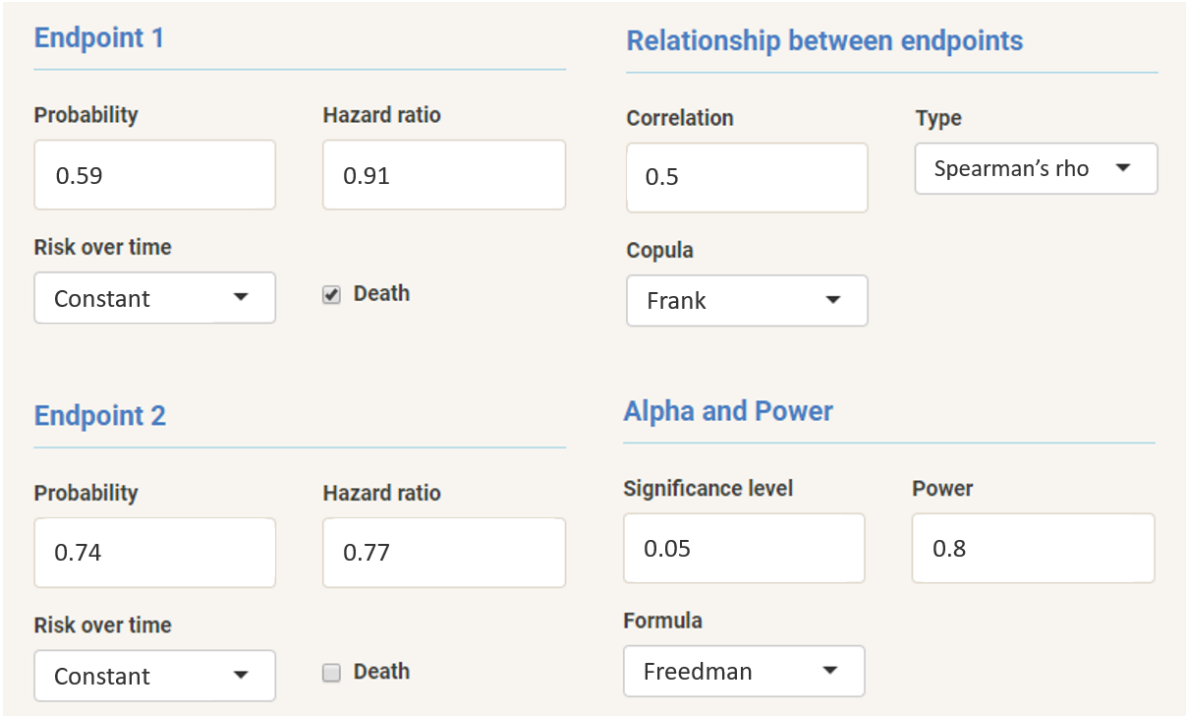
Required sample size for the composite endpoint

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

Zodiac Trial: Input Parameters and Assumptions

Notation

Endpoint 1: ε_1 = Death, Endpoint 2: ε_2 = Disease Progression, Endpoint CE: ε_* = PFS



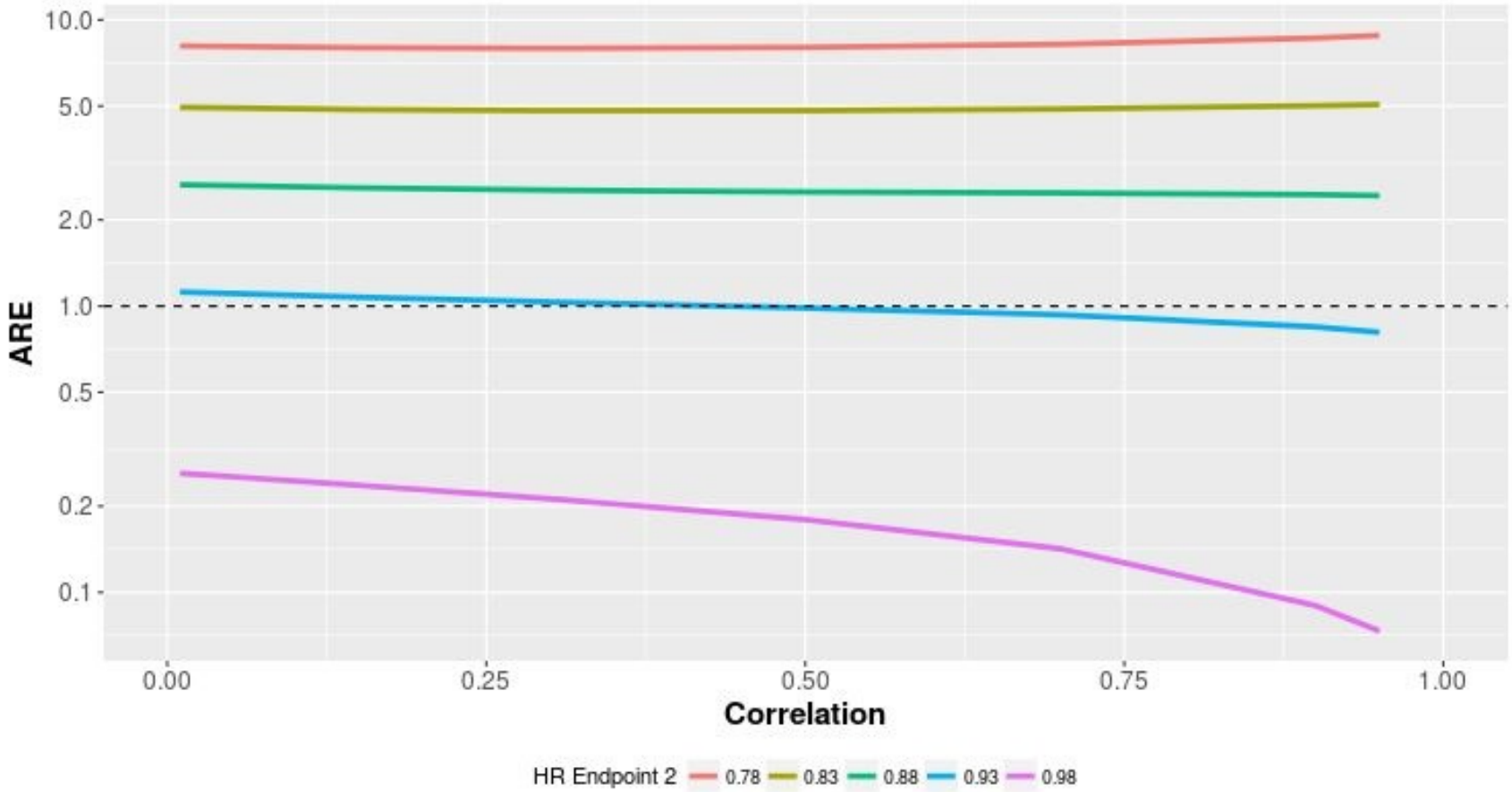
Assumptions

- 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

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



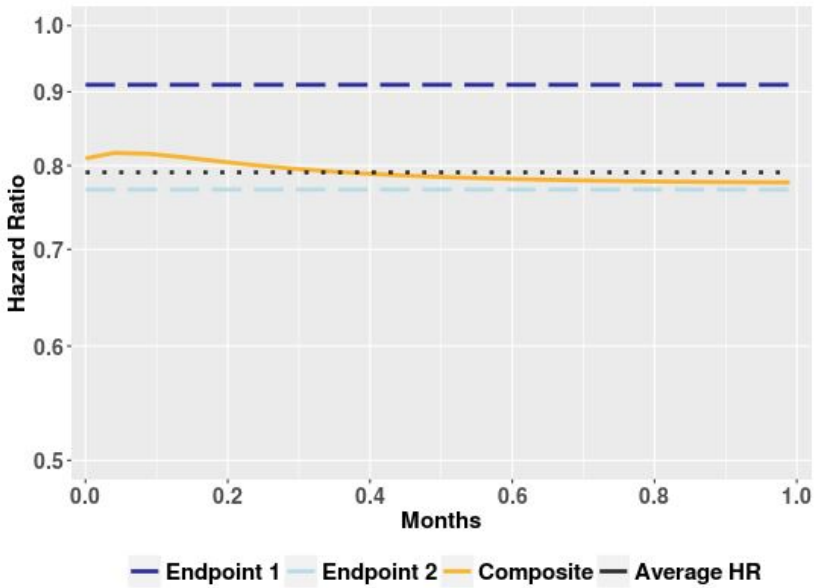
ZODIAC Trial: If we use PFS, how does its effect size behave?

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

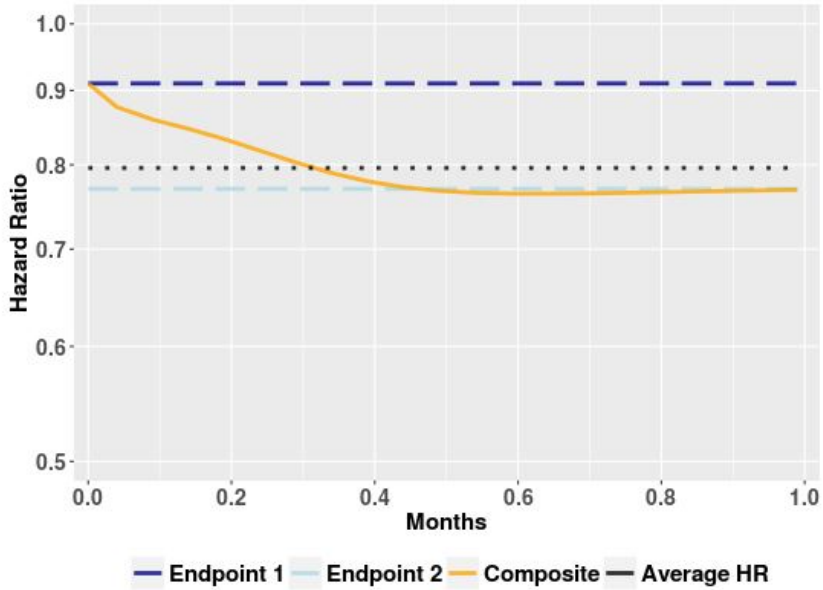
$(p_1, p_2, HR_1, HR_2, \rho)$, marginal hazard behaviours (β_1, β_2), copula to bind T_1 and T_2 and whether death is included (cause specific hazards used instead)

- $HR_1 = 0.91$
- $HR_2 = 0.77$
- $p_1 = 0.59$
- $p_2 = 0.74$
- $\rho = 0.5$
- $\beta_1 = 1$
- $\beta_2 = ?$

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 chose between the composite endpoint and one of its components

2. Effect size

How to specify the expected **treatment effect**? Behavior of the **Hazard ratio** $\mathrm{HR}_*(t)$ 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

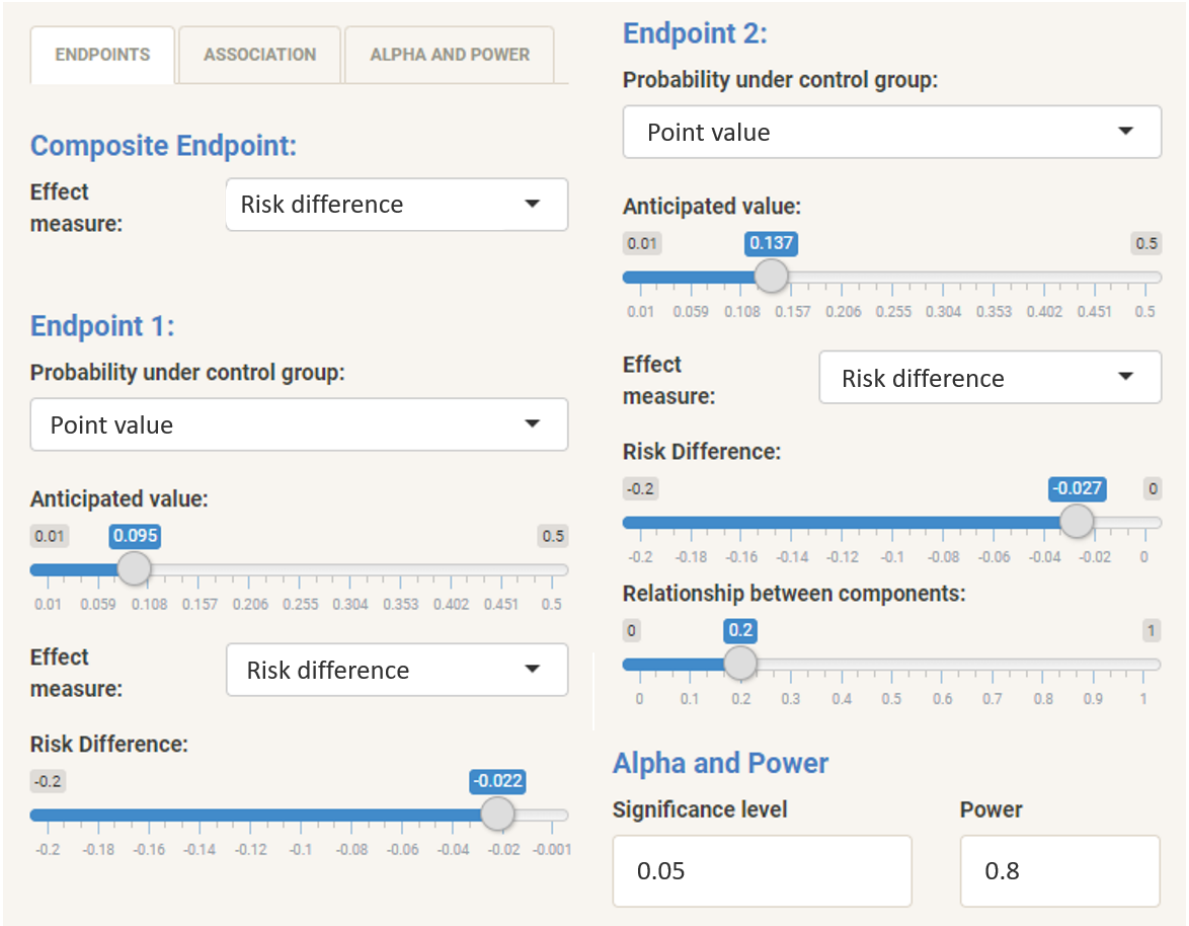
Required sample size for the composite endpoint

(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



Assumptions

Same correlation (ρ) between components in both arms

Getting Sample size for MACE

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:

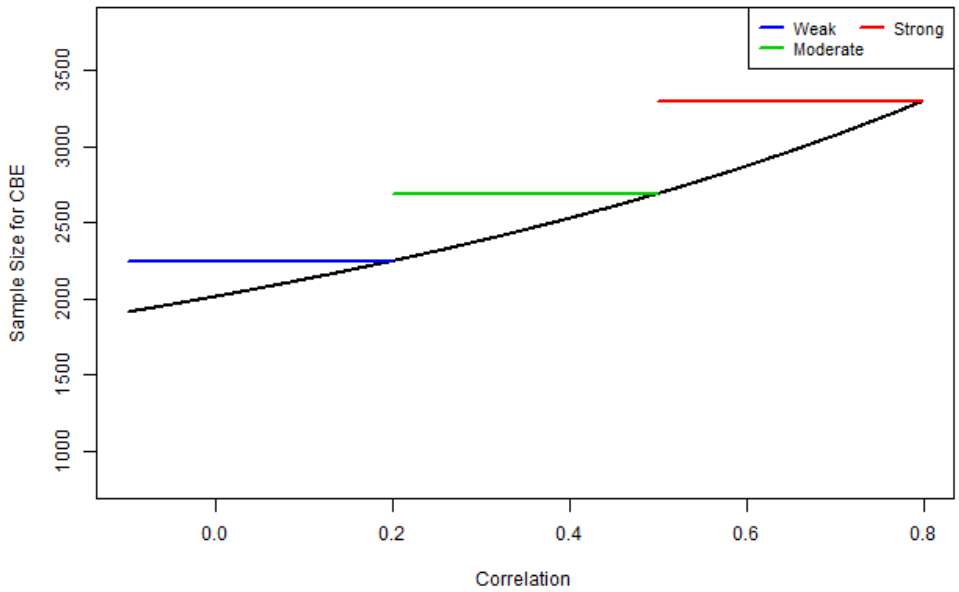
0.137

Effect measure:

Risk Difference

Risk Difference:

-0.027



Sample size is highly sensitive to the association:

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

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

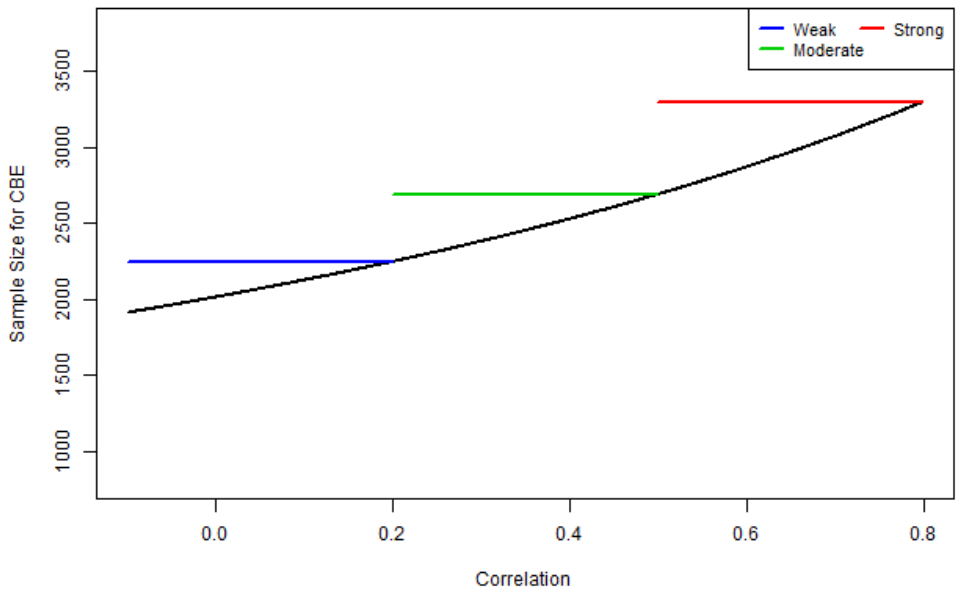
Effect measure:

Risk Difference

Risk Difference:

-0.027

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

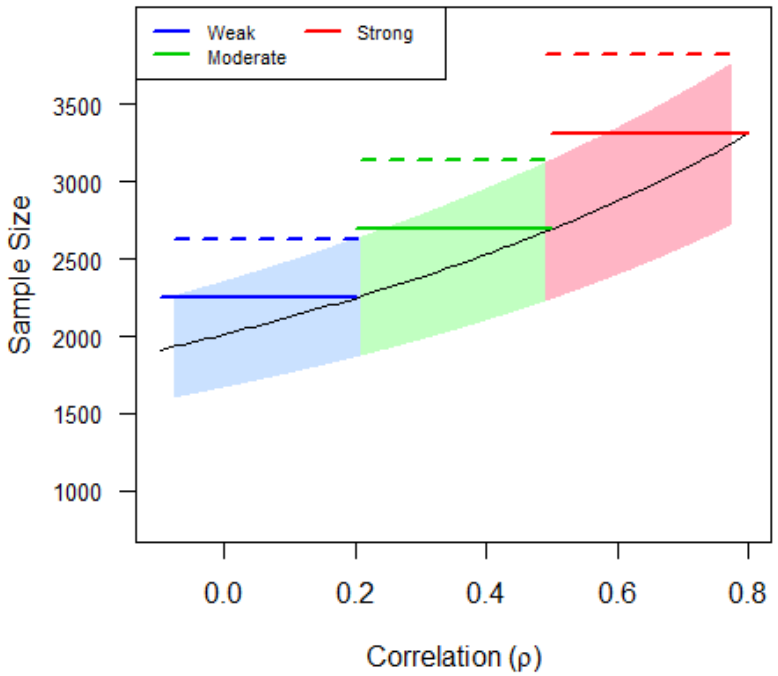


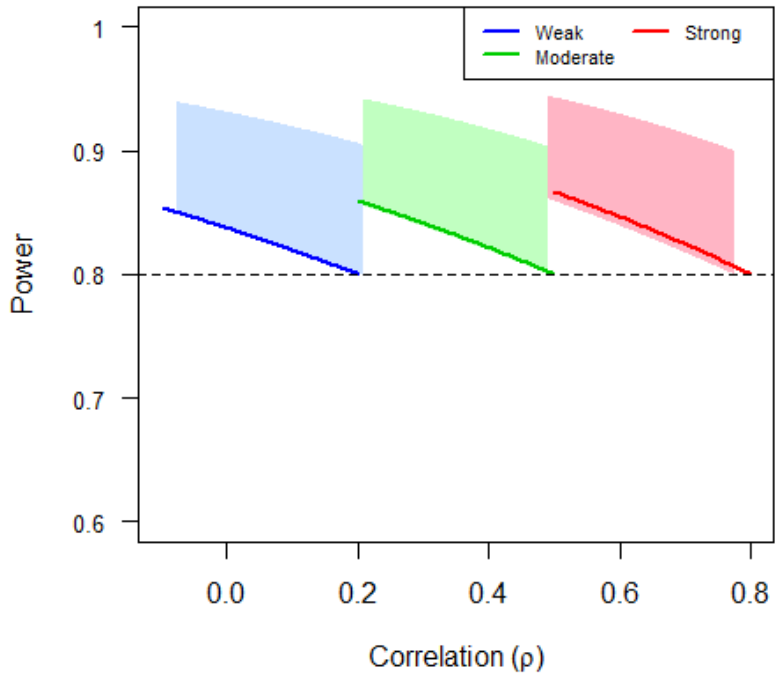
Sample Size and Power for **Intervals** of plausible values for the event rates varying ρ for the TACTICS trial

Intervals of plausible values for the event rates:

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

$I_2^{(0)} = [0.117, 0.157]$ 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 $I_2 = [0.117, 0.157]$.

Future developments (methodological and technical)

- 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

TAKE HOME MESSAGE...

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

This work is partially supported by MTM2015-64465-C2-1-R and MDM-2014-0445 from Spanish Ministry of Economy and Competitiveness (Spain) and 2017 SGR 622 (GRBIO) from Generalitat de Catalunya