Selecting the primary endpoint in a randomized clinical trial with **CompARE**. A cardiovascular case study

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Primeras Jornadas Científicas de Estudiantes de la SEB
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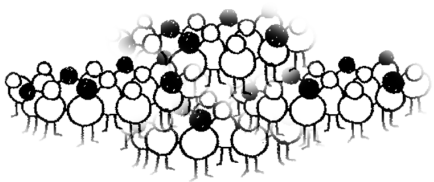
Outline and goals

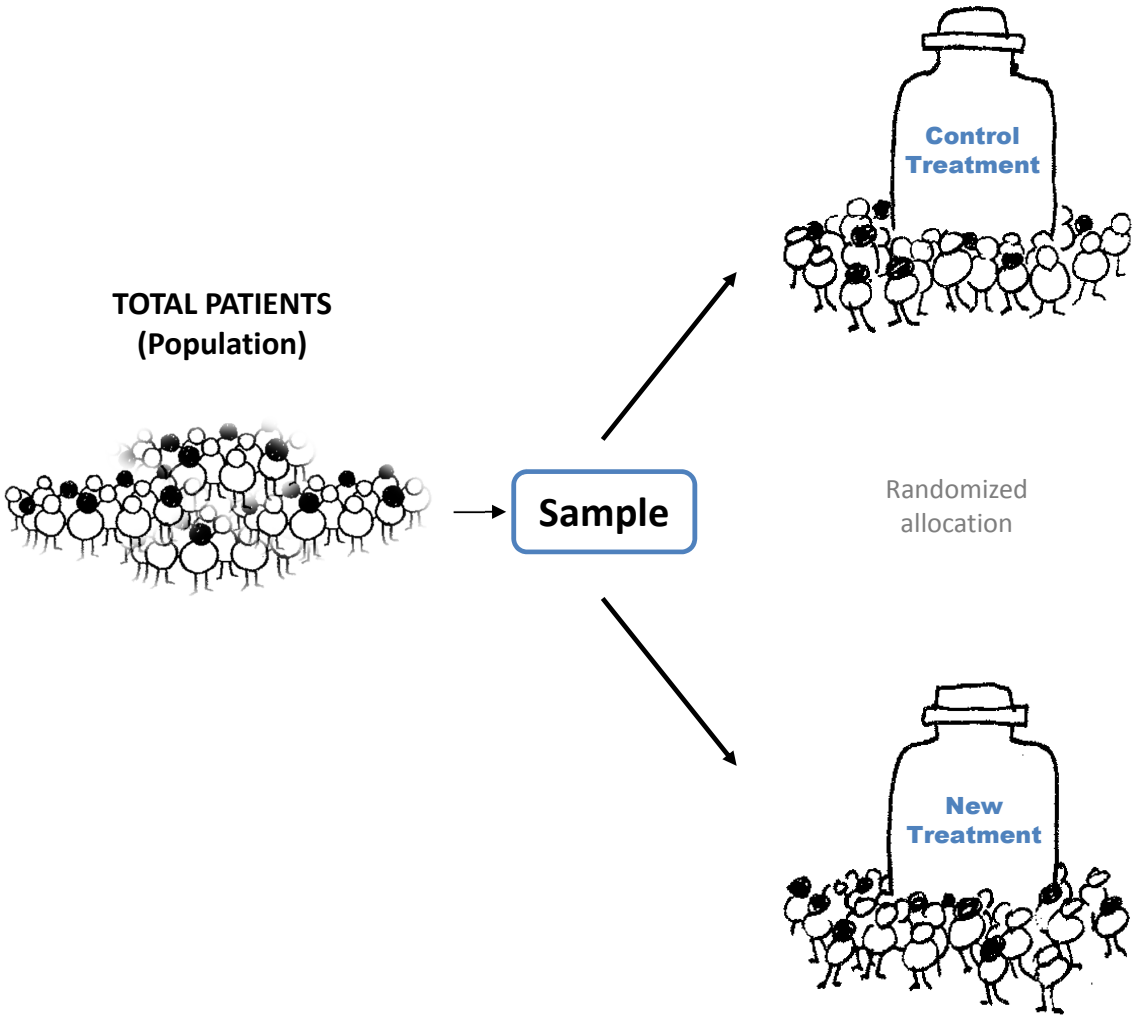
1. Clinical Trials framework and Composite Endpoints
2. Statistical methodology
3. **CompARE**: Web-based platform to help in the decision between CE or a component as the primary endpoint
4. Examples from cardiovascular area
5. Extensions of CompARE

Clinical Trial Scheme

TOTAL PATIENTS
(Population)



Clinical Trial Scheme



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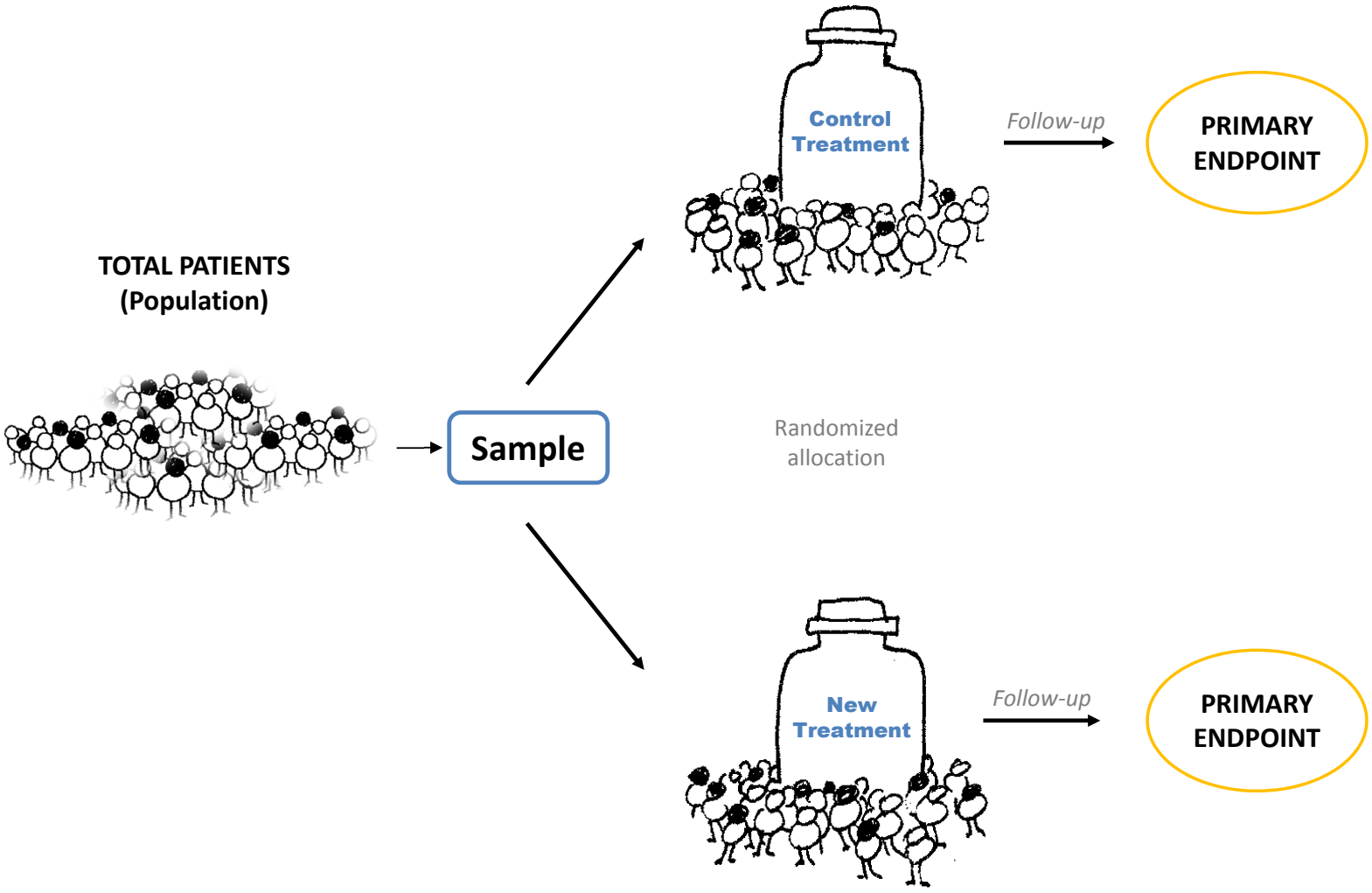


Clinical Trial Scheme

Sample

Randomized allocation

Follow-up

PRIMARY ENDPOINT

Follow-up

PRIMARY ENDPOINT

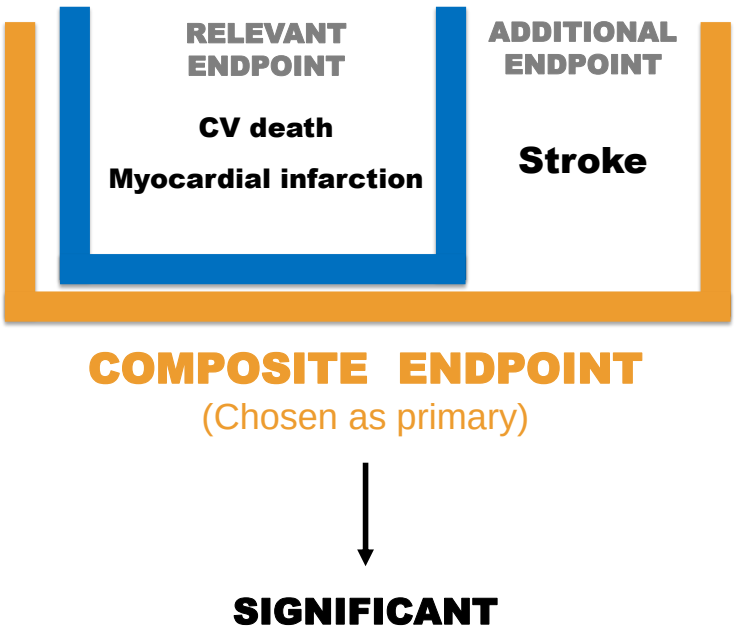
Dilemma?

Composite endpoint
(Death + Stroke)

A component
(Death)

Examples involving Composite endpoints

- **LIFE[1] study:**
  - Control group ($n = 4588$)
  - Losartan ($n = 4605$)



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Examples involving Composite endpoints

- **LIFE[1] study:**
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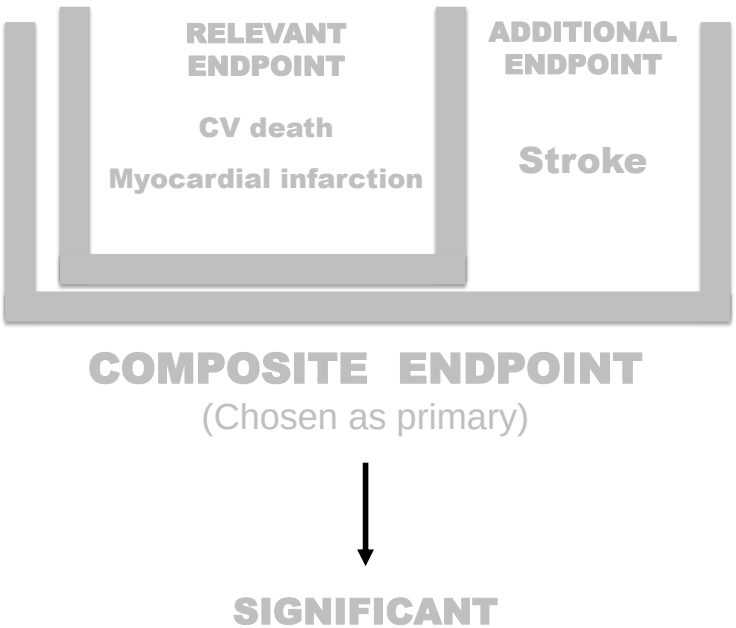
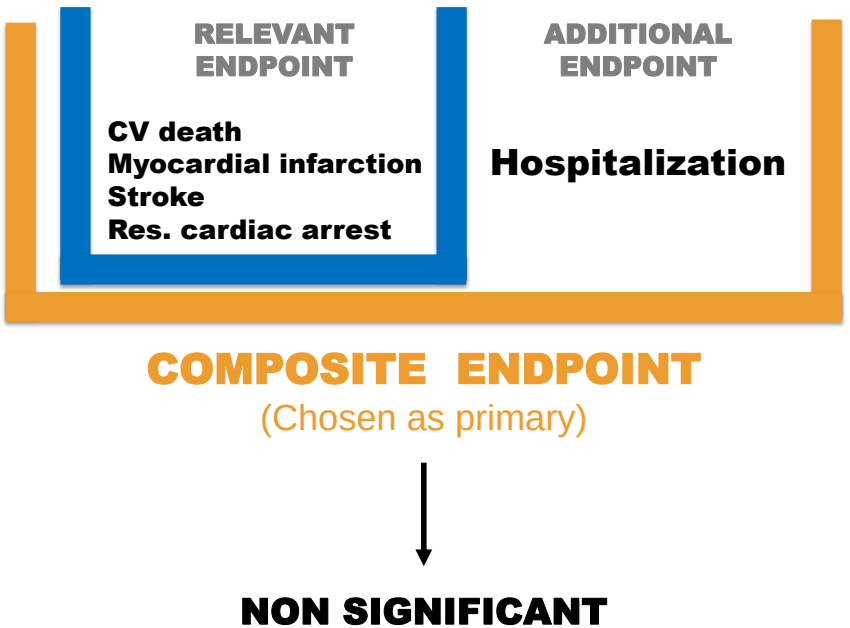
  - Losartan ($n = 4605$)
- **ARISE[2] trial:**
  - Control group ($n = 3066$)
  - Succinobucol ($n = 3078$)





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Composite Endpoints

Clinical concerns

- Medical meaning of the composite
- Relevance with the objectives of the study
- Similar expected effects on each component

Statistical concerns

- Address the problem of multiple comparisons
- Avoid bias due to competing risks
- Observe a higher number of occurrences

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Statistical concerns

- Address the problem of multiple comparisons
- Avoid bias due to competing risks
- Observe a higher number of occurrences

  and CAN (but not always)
- Reduce sample size
- Increase power

Survival Analysis and the Logrank test

- **Relevant endpoint**

  $H_0 : S_R^{(0)}(t) = S_R^{(1)}(t)$

  Logrank Test Statistic Z_R:
  $Z_R \sim N(0,1)$ under H_0
  $Z_R \sim N(\mu,1)$ under H_1

- **Composite endpoint**

  $H_0 : S_*^{(0)}(t) = S_*^{(1)}(t)$

  Logrank Test Statistic Z_*:
  $Z_* \sim N(0,1)$ under H_0
  $Z_* \sim N(\mu_*,1)$ under H_1

The Asymptotic Relative Efficiency (ARE)

- When $ARE(Z_*, Z) > 1 \Rightarrow$ the composite endpoint should be used.

[1] Gómez G. and Lagakos S.W. Statistical considerations when using a composite endpoint for comparing treatment groups (2013). Statistics in Medicine, 32, 719–738.

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- Relationship between ARE and sample sizes to achieve the same power:

$$\mathrm{ARE}(Z_*, Z) = \frac{n}{n_*} \tag{1}$$

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$$\mathrm{ARE}(Z_*, Z) = \left(\frac{\mu_*}{\mu}\right)^2 = \frac{\left(\int_0^1 \log\left\{\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right\} f_*^{(0)}(t)dt\right)^2}{(\log \mathrm{HR_R})^2 (\int_0^1 f_*^{(0)}(t)dt)(\int_0^1 f_R^{(0)}(t)dt)} \tag{2}$$

Required parameter values to calculate ARE

- HR_R and p_R: Hazard Ratio and probability of observing the Relevant endpoint (RE) in control group.
- HR_A and p_A: Hazard Ratio and probability of observing the Additional endpoint (AE) in control group.
- ρ: Spearman's coefficient between T_R and T_A (Time to RE and AE respectively).

CompARE interface

- Free and easy to use
- Knowledge of R not needed
- Accessible anywhere (laptop/mobile/tablet)
- Compatible with any operating system and browser
- Complete users' guide documentation

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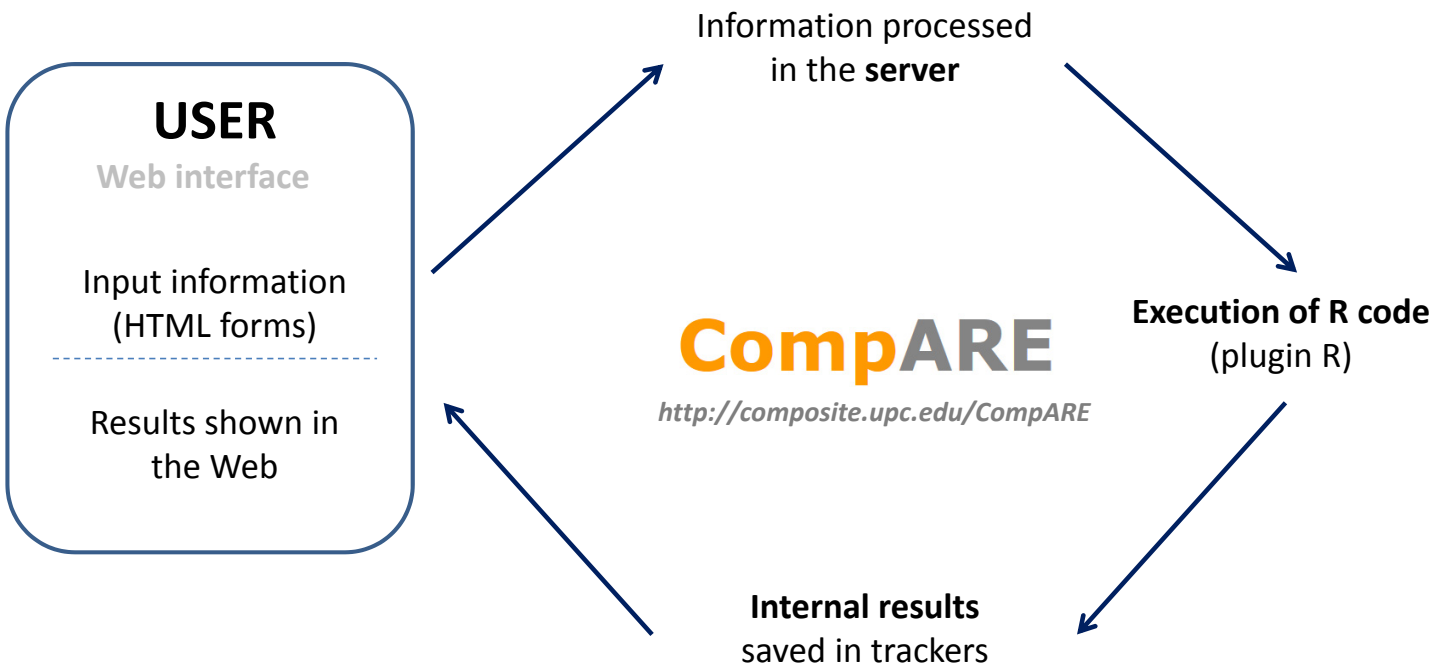


Data from LIFE study (Losartan treatment)

CompARE *Universitat Politècnica de Catalunya - BarcelonaTECH*

HOME | HELP | PERSONAL INFORMATION | ABOUT

Information about all the candidate endpoints for your trial

(You can modify the parameter values and run it again)

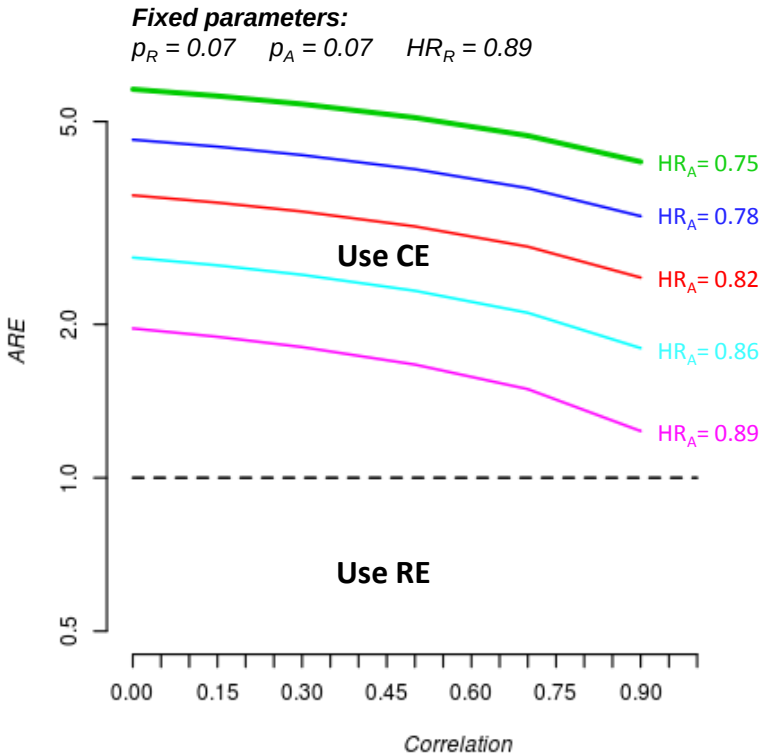
Candidate endpoint *E*	Terminating? (click if yes)	Probability of observing *E* in control group	Hazard Ratio	Type of endpoint	Definition of the Composite
CV mortality	☑	0.05	0.89	Relevant component	☑
Myocardial infarction	☐	0.04	1.07	Relevant component	☑
Stoke	☐	0.07	0.75	Additional component	☑

Advanced Information (Optional)

Shape parameter of the Weibull Distribution

Relevant endpoint	Increasing Hazard Rate (β: 2)
Additional endpoint	Increasing Hazard Rate (β: 2)
Correlation	Moderate (ρ: 0.5)

Graphical results



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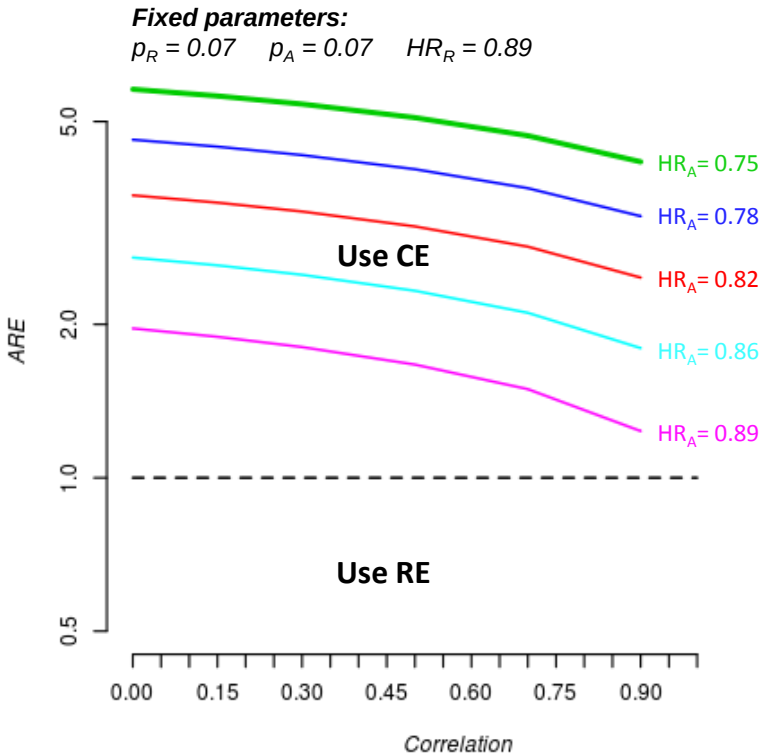
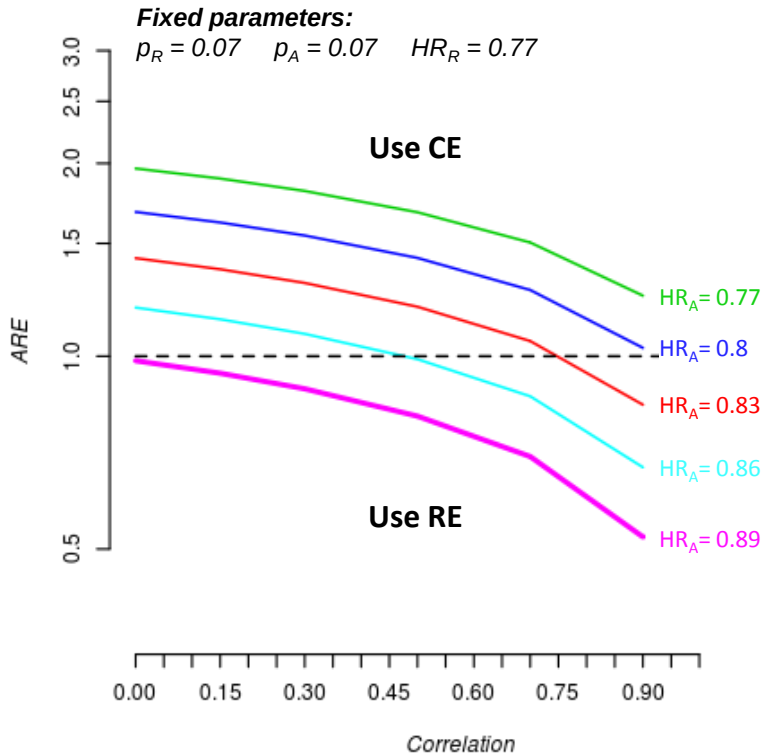
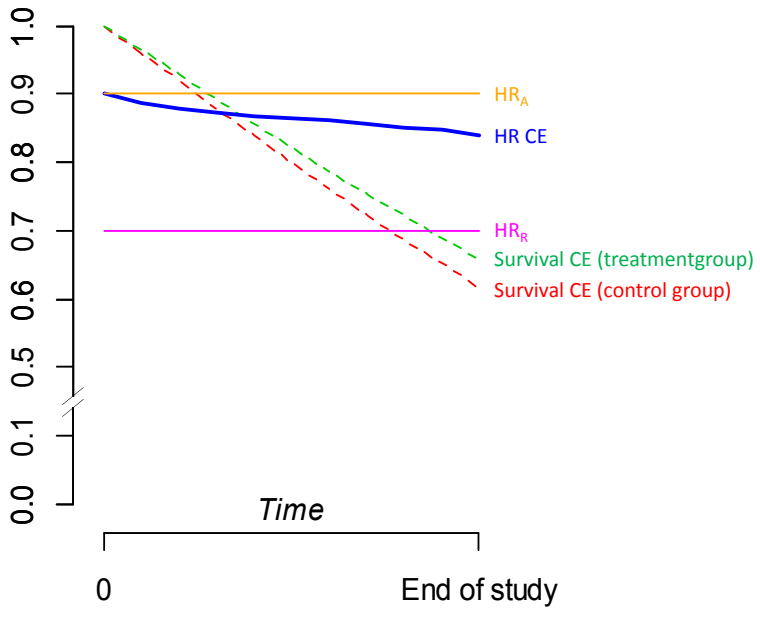




Other outputs

- **Survival and Hazard Ratio functions**



- **Numerical results in tables**

ARE results depending on different correlation values and Hazard Ratios

Fixed parameters:	
Probability RE (Control group)	0.15
Probability AE (Control group)	0.3
Hazard Ratio RE	0.7
Distribution RE	Increasing Hazard Rate
Distribution AE	Constant Hazard Rate (exponential)

Hazard Ratio AE	Correlation	ARE	Recommendation
0.9	0	0.64	Use RE
0.9	0.15	0.56	Use RE
0.9	0.3	0.49	Use RE
0.9	0.5	0.39	Use RE
0.9	**0.7**	**0.3**	**Use RE**
0.9	0.9	0.21	Use RE
0.7	0	2.78	Use CE
0.7	0.15	2.59	Use CE
0.7	0.3	2.4	Use CE
0.7	0.5	2.18	Use CE
0.7	0.7	1.99	Use CE
0.7	0.9	1.9	Use CE

- **Reported recommendations in text**
- **List of previous results**

Ongoing extensions

- Computations when both RE and AE include Death
- Different copulas other than Frank's
- Combined probabilities and hazard ratios

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- **Combined probabilities and hazard ratios**

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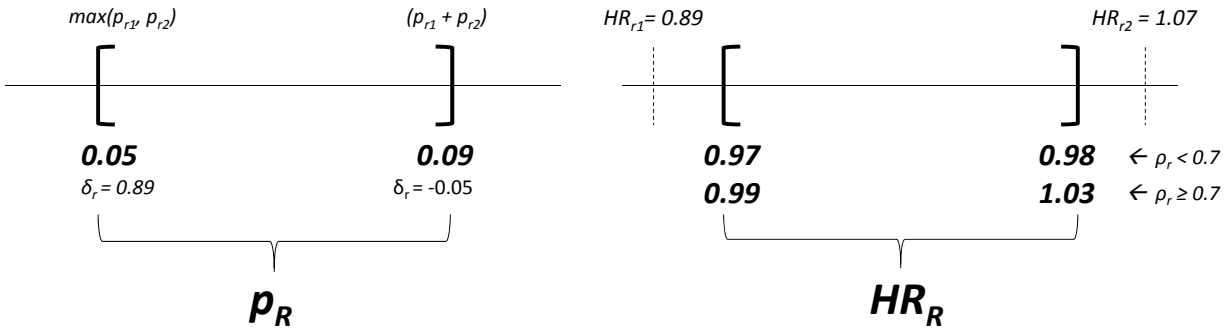

Concluding Remarks and Future Extensions

- Importance of choosing the Primary endpoint in a RCT
- ARE method to choose a Composite endpoint or a component as Primary
- CompARE: Useful tool for Clinicians and Researchers

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- Incorporate sample size calculations
- Possibility to change assumptions by the user (e.g. Distribution laws)
- Binary outcomes
- Improve output results (Dynamic plots)
- Feedback from national/international colleagues

Thanks to:


grup de recerca en anàlisi
estadística de la supervivència
grass


GRBIO


UPC


BIOstatnet
RED NACIONAL DE BIOESTADÍSTICA


INTERNATIONAL BIOMETRIC SOCIETY
SEB

Some references


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