Decision tool and Sample Size Calculator for composite endpoints

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Summary Points:

- This article considers the combination of two binary or two time-to-event endpoints to form the primary composite endpoint for leading a trial.
- It discusses the relative efficiency of choosing a composite endpoint over one of its components in terms of: the frequencies of observing each component; the relative treatment effect of the tested therapy; and the association between both components.
- We highlight the very important role of the association between components in choosing the most efficient endpoint to use as primary.
- For better grounded future trials, we recommend trialists to always reporting the association between components of the composite endpoint
- Common fallacies to note when using composite endpoints: i) composite endpoints always imply higher power; ii) treatment effect on the composite endpoint is similar to the average effects of its components; and iii) the probability of observing the primary endpoint increases significantly.

1. INTRODUCTION

Choosing the primary endpoint (PE) in a randomized controlled trial (RCT) is a critical decision in the design phase. Composite endpoints are defined as the occurrence of any of the relevant events in trials with binary response and as the time from randomization to the first observed event among all components in time-to-event studies. Some examples are the composite of death or myocardial re-infarction and major adverse cardiovascular events (MACE) generally defined as a composite of cardiovascular death, myocardial infarction, stroke and target vessel revascularization.

What are the reasons for using a CE? On the one hand, taking into account multiple outcomes altogether could provide a broader overview of an intervention's efficacy (1). On the other hand, if the event rates are too low, it could increase the study power. However, CEs also hide some drawbacks. For instance, the tested intervention should have a similar effect on all the components while none of them should be affected negative (2). Moreover, having more outcomes does not necessarily imply an increase in power: small intervention effects on one component could mask significant effects on others (3) or strong associations may reduce the joint information.

We discuss the gain in efficiency of adding endpoints to form a primary CE rather than simply using a single relevant endpoint. We provide a multitask tool named CompARE that can be freely access through `https://cinna.upc.edu/compare/` as an aid for a more well-informed decision. The code of the functions implemented in this web app is available in GitHub at `https://github.com/CompARE-Composite/Functions`. CompARE allows to check the efficiency of different designs with more than one outcome and provides a calculator to get the required sample size based on several CEs configurations among other features. This will be illustrated through two RCT published in NEJM and European Heart Journal, respectively (4,5).

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List of abbreviations

- ARE: Asymptotic Relative Efficiency
- ε_1, ε_2, ε_*: Relevant event, ε_1; Additional event, ε_2; Composite event, ε_*, defined as ε_1 or ε_2.
- HR: Hazard Ratio
- PE: Primary Endpoint
- OS: Overall survival
- MI: Myocardial infarction

2. RELATIVE EFFICIENCY OF USING COMPOSITE ENDPOINTS

Should we use the most relevant endpoint (such as overall survival, OS) as the PE for a two-arm RCT? Or should we base our trial on a CE that includes an additional endpoint (such as myocardial re-infarction)? Both endpoints are capable of measuring the treatment effect in the same direction, are of interest to the investigator but they are not equally efficient.

What does efficiency mean when it refers to an endpoint that may be chosen for testing a therapy or treatment? According to the Oxford dictionary, a system is efficient when it “achieves maximum productivity with minimum wasted effort or expense”. A hypothesis testing procedure based on a given endpoint is efficient when it can be influenced by the treatment achieving maximum power for a given sample size. The efficiency is then a measure of the quality of a given test based on an endpoint, while the relative efficiency between two endpoints is determined by their efficiency ratio. Since often we can only assess the efficiency of a statistical test for large enough sample sizes, we use the asymptotic relative efficiency (ARE) as the principal comparison measure. This measure has been studied in a time-to-event framework (6) as well as in a binary setup (7) and it has been used (8) to assess, in the cardiovascular research area, the characteristics that a potential endpoint should have to be part of the CE leading the trial.

Suppose that, two potential endpoints could satisfactorily answer the study’s primary clinical question: we could use a relevant event, say ε_1, or the composite event (ε_*), say ε_1 or ε_2, where ε_2 is some additional endpoint. The ARE measure can be roughly interpreted as the ratio of the required sample sizes using ε_1 versus ε_* to attain the same power for a given significance level (9) yielding the following criterion: whenever ARE >1, choose ε_* as PE to guide the study; otherwise, use ε_1.

To calculate the ARE we need to anticipate: the frequencies of observing events ε_1 and ε_2 in the control group; the relative treatment effect given by either the hazard ratios (HR) –survival outcome– or risk differences –binary outcome– and a measure of the association between components. In very general terms, one should use the CE (ARE>1) if the relative effect of treatment on the additional endpoint is greater or about the same as that on the relevant endpoint. Nevertheless, other scenarios such as those for slightly smaller relative effect of treatment on the additional endpoint together with low frequencies of observing the relevant endpoint, might yield ARE>1, thus, making the composite endpoint more efficient. Furthermore, as we discuss next, the association between ε_1 and ε_2 plays a major role when computing the ARE. The ability to make a well-informed decision can be aided by a simple and friendly tool, such as CompARE, which allows calculating the ARE in various clinical trial scenarios.

3. ASSOCIATION BETWEEN THE COMPONENTS OF THE COMPOSITE ENDPOINT

The association between ε_1 and ε_2 plays a major role when computing the ARE. Two endpoints are positively associated when a large value of one implies a large value of the other, and vice versa.

The association between two binary outcomes can be measured by means of Pearson’s correlation, although the conditional probability of one, given the other, might furnish a more natural and interpretable understanding of association. When we wonder about the percentage of patients ends up suffering a stroke after having a myocardial infarction (MI), the interpretation is quite clear in terms of conditional probability. The positive and linear relationship between the correlation coefficient and the conditional probability allows to use the estimated conditional probability to guess the correlation. For instance, if the frequency of having a MI and suffering a stroke are roughly equal and very low (say, less than 5%), the correlation between them is approximately equal to the proportion of patients having a MI among those that had a stroke.

ARE insights

- The clinical question could be satisfactorily answered by events ε_1 and $\varepsilon_* = \varepsilon_1$ or ε_2, where ε_2 is some additional endpoint.
- ARE quantifies how much more efficient the composite endpoint ε_* is over ε_1 as the primary endpoint of the study:
  - If ARE >1, choose ε_* to guide the study;
  - If ARE <1, base the study on ε_1.
- To compute ARE, we need to anticipate:
  - frequencies of observing ε_1 and ε_2 in the control group,
  - relative treatment effect given by the hazard ratios (in a survival trial) or risk differences (in a binary trial). In the survival setting, additional assumptions should be made.
  - a measure of the association between ε_1 and ε_2.

The association between the time-to-event outcomes for ε_1 and ε_2 is a little bit "tricky" in the presence of competing risks, when one outcome could prevent the observation of the other. The ARE method is based on a joint copula model built on the cause specific hazards for times to ε_1 and ε_2 and on Spearman's rho correlation between these times. We strongly remark here that the anticipation of Spearman's rho is only done for the purpose to obtain precise sample size calculations and not assumed to be used or computed in the analysis phase when it makes no sense to get the association between times to ε_1 and ε_2 when one of them is death.

It has been shown (6,7) that the efficiency of using a CE rather than using its more relevant component decreases as the composite components become more associated; or, in other words, the more correlated the components are, the larger the sample size needed for the trial (9) and using the CE might not be worthwhile.

The association between the components of the composite endpoint has a significant impact both on the probability of observing the composite endpoint and on the efficiency of the composite endpoint as a primary endpoint. Therefore, it is of utmost importance to consider how the components of the composite endpoint are associated, quantify this association and report them in all documents and summaries derived from the trials.

4. CASE STUDIES USING COMPARE

We illustrate the PE decision using two RCTs and with the aid of CompARE, which is useful for different purposes as shown in Figure 1. CompARE is a comprehensive and freely available web-tool intended to provide guidance on how to deal with composite endpoints in the planning stage of a randomized controlled trial. CompARE can also be used to:

1. Choose the best primary endpoint to lead the trial. CompARE computes the ARE to quantify the gain in the efficiency of using –as the primary endpoint– a composite endpoint over one of its components.
2. Specify the treatment effect for the composite endpoint based on the marginal information of the composite components and to study the performance of the composite parameters according to these. In a survival trial, it can also evaluate the proportional hazards assumption for the composite endpoint.
3. Determine the sample size for different situations, such as when the association between composite components is unknown or when the hazards are not proportional.
4. Calculate and interpret the different association measures among the composite components.

The code to reproduce the following two case studies is available in GitHub.

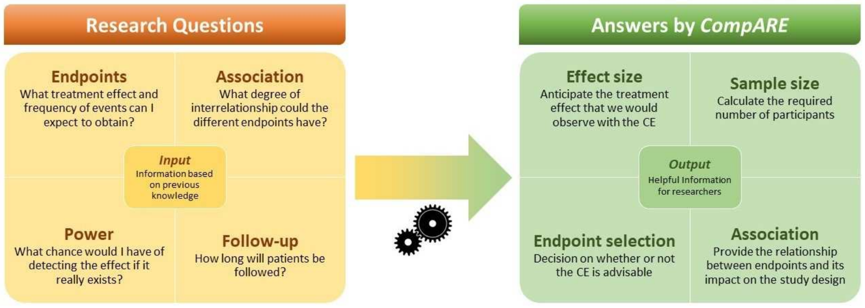

Research Questions
Endpoints
What treatment effect and frequency of events can I expect to obtain?
Association
What degree of interrelationship could the different endpoints have?
Input
Information based on previous knowledge
Power
What chance would I have of detecting the effect if it really exists?
Follow-up
How long will patients be followed?
Answers by CompARE
Effect size
Anticipate the treatment effect that we would observe with the CE
Sample size
Calculate the required number of participants
Output
Helpful information for researchers
Endpoint selection
Decision on whether or not the CE is advisable
Association
Provide the relationship between endpoints and its impact on the study design

Figure 1: CompARE scheme with the inputs to be provided by the researcher and the outputs returned by the application.

4.1. TUXEDO trial: binary endpoints

The TUXEDO study was a RCT aimed at comparing paclitaxel-eluting stents (control group) with everolimus-eluting stents (intervention group) (4). The PE was target-vessel failure (ε_*), defined as a composite of cardiac death, target vessel MI or ischemia-driven target-vessel revascularization at 1-year of follow-up. The secondary endpoints were, among others, the ischemia-driven target-lesion revascularization (ε_1, revascularization for short) and the endpoint of cardiac death or target-vessel MI (ε_2, death or MI for short). The TUXEDO protocol was based on the results of the SPIRIT IV trial (10), which faced similar research questions and considered the same PE and that we will use as reference values for illustrative purposes. The association between the different outcomes was not reported, nor was the number of patients who had more than one event.

Would it have been preferable to consider revascularization (ε_1) instead of the CE of target-vessel failure (ε_*) as PE? We discuss it considering that the frequency of ε_1 and ε_2 in the control group were 5.9% and 3.2%, respectively. Everolimus-eluting stents as compared with paclitaxel-eluting stents resulted in a 1.96 percentage-point absolute reduction in ε_1 and a 0.98 percentage-point absolute reduction in ε_2.

Association	Correlation	Conditional probability ε_1 given ε_2	Conditional probability ε_2 given ε_1	Probability of observing ε_*	Percentage-point absolute reduction ε_*	Total Sample Size
Weak	0.1	0.19	0.1	0.08	2.7	2,187
Moderate	0.4	0.58	0.31	0.07	2.3	2,561
Strong	0.7	0.97	0.52	0.06	2.0	3,076

Table 1: Probability of target-vessel failure (ε_*) and total sample size to achieve a power of 80% at a significance level of 0.05 in a design with ε_* as PE based on the SPIRIT IV trial values and for different degrees of association between ε_1 and ε_2

Table 1 presents three scenarios according to weak, moderate, strong degrees of association between revascularization and death or MI. The strength of association is provided both in terms of the correlation coefficient (0.1, 0.4, 0.7) and as the conditional probability of ε_2 given a ε_1. For each of these scenarios and based on the values provided by the SPIRIT IV trial, the probability of observing ε_* in the control group ranges between 6% and 8%; and the expected absolute reduction for ε_* takes values between 2.3 and 2.9. Observe that both the probability and the expected effect for ε_* decrease as the association increases, and this pattern is always found (11,12). We have also computed the required total sample size for a trial with ε_* as PE. Notice that, as the association between the composite components gets larger, the sample size is increasingly higher.

Figure 2 shows that the efficiency of using ε_* as PE rather than ε_1 decreases as the components become more correlated. Indeed, revascularization is preferred over target-vessel failure when ε_1 and ε_2 are strongly associated. To study the extent to which adding ε_2 affects the PE choice, we consider several effect values for ε_2: for a given correlation, the ARE increases as the anticipated treatment effect in ε_2 gets larger.

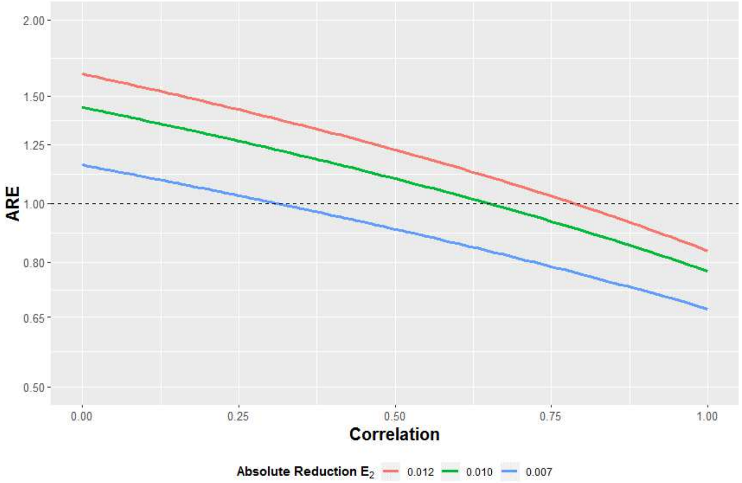
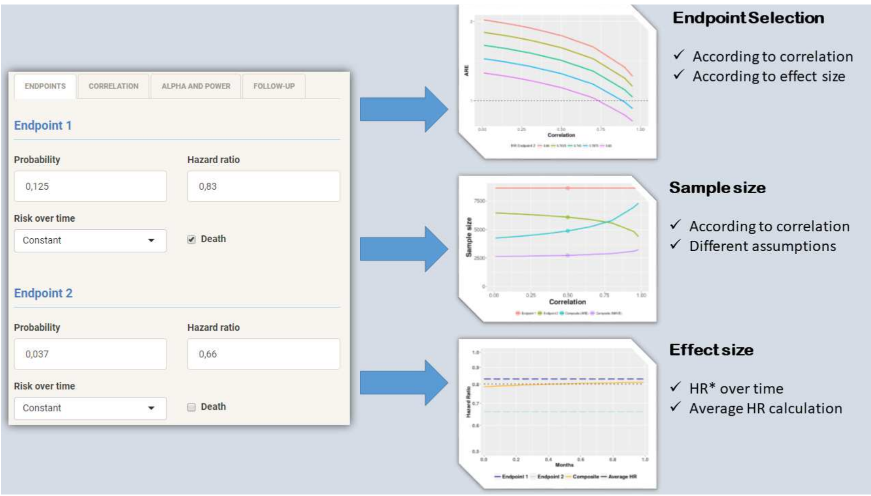


Figure 2: ARE values depending on the correlation (horizontal axis) and the treatment effect of the additional endpoint (colored lines).

4.2. *OASIS-6 trial: time-to-event endpoints*

Odlgren et al. (5) tested fondaparinux treatment vs. placebo or unfractionated heparin, in a pre-specified subgroup of 2,867 patients not receiving reperfusion treatment in the OASIS-6 trial. The primary outcome was the composite endpoint (ε_*) of death or myocardial re-infarction at 30 days. The observed frequency in the control group was 0.125 for OS (ε_1) and 0.037 for myocardial re-infarction (ε_2), and the estimated HRs were 0.83 for ε_1 and 0.66 for ε_2.

If a new similar study was planned, should we use the composite endpoint (ε_*) to lead the trial or should we stick to OS as the PE? Figure 3 shows how CompARE can help to discuss the efficiency of using death or myocardial re-infarction as PE (see also Figure 4), to compare sample sizes and to illustrate effect sizes for several scenarios with different HRs (between 0.65 and 0.90) for ε_2 and several degrees of association.



Endpoint 1

Probability: 0,125

Hazard ratio: 0,83

Risk over time: Constant

☑ Death

Endpoint 2

Probability: 0,037

Hazard ratio: 0,66

Risk over time: Constant

☐ Death

Endpoint Selection

✓ According to correlation
✓ According to effect size

Sample size

✓ According to correlation
✓ Different assumptions

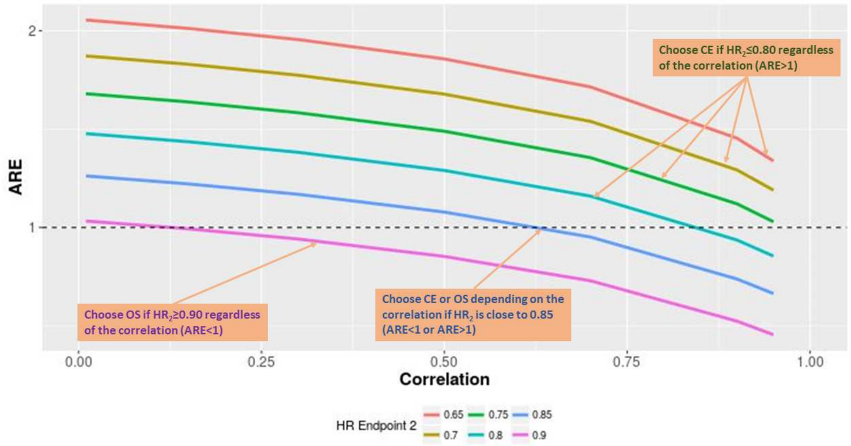
Effect size

✓ HR* over time
✓ Average HR calculation

Figure 3: Screenshots of CompARE using the information from the OASIS-6 Trial.

Figure 4 (self-explained) shows the influence of correlation on the ARE value and, consequently, can be used as a criterion to choose between OS or the CE formed by death (ε_1) and Myocardial re-infarction (ε_2). The ARE values (vertical axis) depend on the Spearman correlation (horizontal axis) and the treatment effect of the additional endpoint (colored lines). Cause-specific hazard function for the time to Myocardial re-infarction (ε_2) and the time to death (ε_1) are assumed constant during the follow-up.

When the PE is based on the time from randomization to ε_*, the behavior of the corresponding cause-specific hazards has to be as well anticipated. Table 2 presents the ARE and the required sample size under five selected scenarios, assuming constant, increasing or decreasing hazards for each outcome and strong correlation between them. ARE is greater than 1 in all scenarios and hence ε_* is always recommended; however sample sizes vary a lot – in a range from 2,682 to 3,381 – exemplifying the impact of the hazard shape over time.



Choose CE if $HR_2 \leq 0.80$ regardless of the correlation (ARE>1)

Choose OS if $HR_2 \geq 0.90$ regardless of the correlation (ARE<1)

Choose CE or OS depending on the correlation if HR_2 is close to 0.85 (ARE<1 or ARE>1)

Figure 4: ARE values depending on the correlation (horizontal axis) and the treatment effect of the additional endpoint (colored lines).

Hazard of death	Hazard of	ARE	Total
	myocardial re-infarction		Sample Size
Increasing ↑	Decreasing ↓	1.84	3,381
Constant ↔	Decreasing ↓	1.90	3,278
Constant ↔	Constant ↔	2.02	3,084
Constant ↔	Increasing ↑	2.18	2,857
Decreasing ↓	Increasing ↑	2.32	2,682

Table 2: ARE and the required sample size to achieve an 80% power at a significance level of 0.05 for detecting differences in the CE, depending on the cause-specific hazard behavior over time for each component: constant (exponential distribution), increasing (Weibull distribution with shape parameter equals 2) or decreasing (Weibull with shape parameter equals 0.5). Other assumed parameters: i) frequencies of 0.125 and 0.05 for death and myocardial re-infarction in the control arm; ii) HRs of 0.83 and 0.66 for OS and myocardial re-infarction; and iii) Spearman's rho correlation between components equal to 0.7, considering Gumbel copula. Sample size calculations are based on the Freedman formula.

5. DISCUSSION

Composite endpoints are commonly used in clinical trials and observational studies. However, contrary to popular belief, composite endpoints only barely increase total event-probability and do not necessarily yield higher power.

The design of a randomized controlled trial involving a composite endpoint needs a careful specification of the expected rates, the treatment effects and the correlation between the components. While the frequencies and relative effects of the primary and secondary endpoints in most of the published clinical trials can often be derived from previous studies, the degree of association between them are seldom disclosed. CompARE can be used to explore different scenarios and for each one calculate the treatment effect for the CE and the needed sample size.

Because the association between the composite components plays an important role in the overall expected frequency of the CE, but also in the statistical power of the study, this information is critical in designing a trial, it has a large impact on the design efficiency, notably on the PE choice and, hence, on the trial's sample size. For example, the SAMPL guidelines (13) enumerate the items to be reported for each type of analysis, but currently do not make any reference to this point. We urge trialists to report, as accurately as possible, all the primary and secondary parameter information as well as a measure of the association between the endpoints considered in the trial.

Acknowledgements

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