EXTENSION OF THE ASYMPTOTIC RELATIVE EFFICIENCY METHOD TO SELECT THE PRIMARY ENDPOINT IN A RANDOMIZED CLINICAL TRIAL

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ABSTRACT

We extend the ARE method proposed in Gómez and Lagakos (2013) devised to decide which primary endpoint to choose when comparing two treatments in a randomized clinical trial. The ARE method is based on the Asymptotic Relative Efficiency (ARE) between two logrank tests to compare two treatments: one is based on a relevant endpoint $\mathcal{E}_1$ while the other is based on a composite endpoint $\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_2$, where $\mathcal{E}_2$ is an additional endpoint. The ARE depends, besides some intuitive parameters, on the joint law of the times T_1 and T_2 from randomization to $\mathcal{E}_1$ and $\mathcal{E}_2$, respectively. Gómez and Lagakos (2013) characterize this joint law by means of Frank's copula. In our work, several families of copulas can be chosen for the bivariate survival function of (T_1, T_2) so that different dependence structures between T_1 and T_2 are feasible. We motivate the problem and show how to apply the method through a real cardiovascular clinical trial. We explore the influence of the copula chosen into the ARE value by means of a simulation study. We conclude that the recommendation on whether or not to use the composite endpoint as the primary endpoint for the investigation is, almost always, independent of the copula chosen.

Key words: Asymptotic relative efficiency; Composite endpoint; Copulas; Logrank; Randomized clinical trial

1 INTRODUCTION

When comparing two treatment groups by means of a randomized clinical trial (RCT), the choice of the primary endpoint is crucial. It is often the case in which several relevant events might be chosen as the primary endpoint for the analysis and the decision on which one to choose might be difficult. Sometimes, the event with the greatest clinical importance is the chosen one while the other events are assessed using secondary analysis. In other situations, two or more events are of comparable importance and, in those cases, it is common to use the union of them as the primary endpoint. In general, the decision on which endpoint to use is, among other criteria, based on the prior knowledge of the frequency of observing the "candidate" events as well as on the anticipated effect that the treatment could have on each event.

Several authors have discussed the advantages and disadvantages of using a composite endpoint from a clinical perspective (Ferreira-González et al., 2007b; Gómez, 2011; Freemantle et al., 2003; Montori et al., 2007; Ferreira-González et al., 2007a). One of the main clinical arguments is that the composite endpoint could capture the net benefit of the intervention, avoiding the need to choose a single main endpoint when different endpoints are of equal importance. From a statistical point of view, two main arguments are: i) a composite endpoint reduces the multiplicity problem that may occur if different endpoints are used separately; and ii) a larger number of events will be observed when using a composite endpoint than for any relevant event alone. However, as it is shown in Gómez and Lagakos (2013), a larger number of events would not necessarily imply a more powerful test for treatment efficacy. Moreover, the use of a composite endpoint could entail certain difficulties such as how to interpret the results of a trial when the primary endpoint is composed of events of different clinical importance. It is also important to keep in mind that a significant treatment effect on the composite endpoint does not necessarily imply an effect on each of the components (Gómez, 2011).

Gómez and Lagakos (2013) have provided a statistical methodology to derive efficiency guidelines for deciding whether to expand a study's primary relevant endpoint $\mathcal{E}_1$ to the composite $\mathcal{E}_*$ of $\mathcal{E}_1$ and $\mathcal{E}_2$, where $\mathcal{E}_2$ is some additional endpoint. This methodology has already been applied to derive recommendations for the choice of the primary endpoint in cardiovascular randomized clinical trials (Gómez et al., 2014). The method they propose is based on the Asymptotic Relative Efficiency (ARE) of a logrank test for comparing treatment groups with respect to the time T_1 from randomization to $\mathcal{E}_1$ versus the time T_* from randomization to $\mathcal{E}_*$. For the computation of the ARE, and among other things to be discussed below, the law of (T_1, T_2) is derived binding the marginals distributions of T_1 and T_2, the time from randomization to $\mathcal{E}_2$, by means of Frank copula.

The choice of the copula is a crucial step in the ARE computations. There are some statistical procedures available to decide which copula fits better existing data (see for example Genest et al. (2009)). However, the methodology developed by Gómez and Lagakos (2013) provides a tool to choose the primary endpoint of a RCT during its design, when the data is still not available and it is not possible to apply such procedures. The recommendation on whether to base the RCT on a relevant endpoint $\mathcal{E}_1$ or use the composite $\mathcal{E}_*$ might heavily depend on this choice. Since different families of copulas might exhibit substantially different dependence structures, even with similar degrees of dependence, it is important to consider other copulas in the construction of the bivariate survival function of (T_1, T_2) and to explore the impact that this choice might have.

The main aim of this paper is twofold: on one hand, it extends the ARE method to other families of copulas, allowing different joint behaviors between T_1 and T_2; on the other, it explores the influence of the copula chosen into the ARE values. Furthermore, it examines the impact that a copula has on the recommendation for the primary endpoint for the RCT. The remainder of this paper is organized as follows. In Section 2, we extend the ARE method to families of copulas other than Frank and introduce a real clinical trial to motivate the problem and to show how to use this method. In Section 3, we study the sensitivity of the ARE values to the choice of the copula. Simulated scenarios have been set up and the ARE values have been compared using different copulas. Finally, we make the concluding remarks in Section 4.

2 THE ASYMPTOTIC RELATIVE EFFICIENCY (ARE) METHOD

This section extends the ARE method to families of copulas other than Frank. We start with the description of the ARE method, continue with a subsection devoted to the construction of joint survival functions given their univariate marginals via a copula model where we introduce and compare Frank, Gumbel, Clayton, Farlie-Gumbel-Morgenstern (FGM), Normal, *t*, Plackett, Galambos, Hüsler-Reiss, Tawn and *t*-EV copulas, with special emphasis to the first three. A third subsection is dedicated to how to compute the ARE values using R. This section ends with a case study concerning a randomized clinical trial designed to test the effect of the antioxidant succinobucol on cardiovascular outcomes in patients with recent acute coronary syndrome.

2.1 Notation and summary of the ARE method

Consider a two-arm randomized study with assignment to an active ($X = 1$) or control treatment ($X = 0$), for example new treatment versus standard of care or placebo. Let us assume that both the relevant endpoint $\mathcal{E}_1$ and the composite endpoint $\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_2$ could answer satisfactorily the study's primary clinical question. Denote by $T_* = \min\{T_1, T_2\}$ the time from randomization to $\mathcal{E}_*$ and assume that T_1 and T_2 are absolutely continuous so that ties cannot occur. Gómez and Lagakos assume in the ARE method that the end-of-study censoring at time τ is the only non-informative censoring cause and, without loss of generality, take $\tau = 1$ for computational purposes. They also assumed that this censoring is identical across treatment groups.

Let Z (similarly Z_*) be the logrank test to compare the two treatment groups with respect to the relevant endpoint $\mathcal{E}_1$ (similarly with respect to the composite endpoint $\mathcal{E}_*$). Denote by $\mathrm{ARE}(Z_*, Z)$ the Asymptotic Relative Efficiency of Z_* versus Z. Efficiency calculations are evaluated on the basis of a sequence of contiguous alternatives to the null hypothesis of no treatment effect, and based on the following assumptions: (i) the correlation between T_1 and T_2 is the same for both treatment groups; (ii) the hazards for T_1 and T_2 between the two treatment groups are proportional. For $i = 1, 2$, let $\lambda_i^{(j)}(t)$ ($j = 0, 1$) be the hazard function of endpoint T_i for treatment group j and denote by $\mathrm{HR}_i = \lambda_i^{(1)}(t)/\lambda_i^{(0)}(t)$ the hazard ratio; and (iii) Weibull distributions have been chosen as the law for T_1 and T_2 with scale parameters $b_1^{(j)}$ and $b_2^{(j)}$ for groups $j = 0, 1$ and shape parameters β_1 and β_2 chosen equal for both groups so that the proportionality of the hazards holds.

Based on the above assumptions, and assuming that the additional endpoint does not contain a terminating event among its components (Censoring cases 1 and 3 in Gómez and Lagakos paper), the expression of the ARE value is as follows

$$\mathrm{ARE}(Z_*, Z) = \frac{\left(\int_0^1 \log\left(\frac{\lambda_*^{(1)}(t;\theta)}{\lambda_*^{(0)}(t;\theta)} \right) f_*^{(0)}(t;\theta)\, dt \right)^2}{(\log \mathrm{HR}_1)^2 \left(\int_0^1 f_*^{(0)}(t;\theta)\, dt \right) \left(\int_0^1 f_1^{(0)}(t)\, dt \right)} \tag{1}$$

where $f_1^{(0)}(t)$ and $f_*^{(0)}(t;\theta)$ are the density functions of T_1 and T_* in group 0, $\lambda_*^{(0)}(t;\theta)$ and $\lambda_*^{(1)}(t;\theta)$ are the hazard functions of T_* in group 0 and group 1, respectively, and θ is a parameter, introduced in Section 2.2, that measures the dependence between T_1 and T_2 in either group.

In order to get a meaningful expression for the ARE given in (1) in terms of interpretable and anticipatable parameters, a relationship between them and $f_1^{(0)}(t)$, $f_*^{(0)}(t;\theta)$, $\lambda_*^{(0)}(t;\theta)$ and $\lambda_*^{(1)}(t;\theta)$ is sought. Gómez and Lagakos use Frank's copula to bind the marginals of T_1 and T_2, and, from there, obtain the law of T_*, and, consequently, expressions for the density and the hazard functions.

After choosing a copula, the ARE value depends uniquely on the survival functions of T_1 and T_2 and on the dependence parameter θ. It can be shown that θ is in one-to-one relationship with Spearman's rank correlation coefficient ρ, and that the marginals can be identified from the following set of parameters: the frequencies p_1 and p_2 of observing the endpoints $\mathcal{E}_1$ and $\mathcal{E}_2$ in treatment group 0, the relative treatment effects on $\mathcal{E}_1$ and $\mathcal{E}_2$ given by the hazard ratios HR_1 and HR_2, and, the shape parameters β_1 and β_2 of the Weibull distributions used as the law for T_1 and T_2, respectively.

Given these set of parameters, one might compute the ARE value and decide the most efficient endpoint between $\mathcal{E}_1$ ($\mathrm{ARE} \leqslant 1$) and $\mathcal{E}_*$ ($\mathrm{ARE} > 1$). We illustrate the ARE method assuming that the

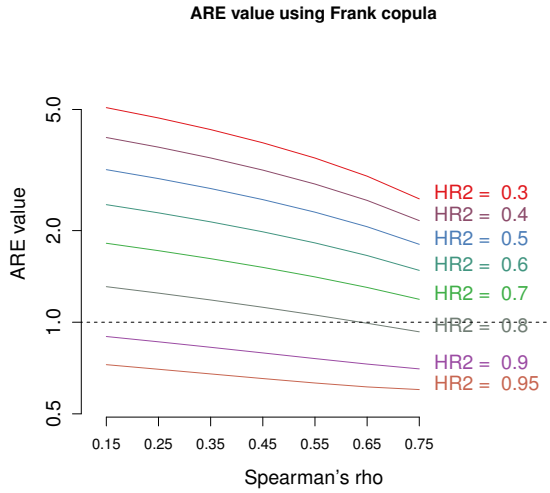

Figure 1: ARE values calculated using Frank copula for parameters $p_1 = 0.2$, $p_2 = 0.1$, $HR_1 = 0.8$ and $\beta_1 = \beta_2 = 1$ and for different values of HR_2 and ρ.

probability of observing $\mathcal{E}_1$ and $\mathcal{E}_2$ is, respectively, $p_1 = 0.2$ and $p_2 = 0.1$ and that the expected effect of the treatment on $\mathcal{E}_1$, given by the hazard ratio, is set to $HR_1 = 0.8$. Figure 1 plots the ARE values for different values of HR_2, the effect of the treatment on $\mathcal{E}_2$; different values of ρ, the correlation between T_1 and T_2 in group 0; and for the particular case in which the hazards are constant ($\beta_1 = \beta_2 = 1$). This figure provides an extra tool to decide between $\mathcal{E}_1$ and $\mathcal{E}_*$, even when the values of HR_2 or ρ are only known within a range.

It is worth noting that the above set of assumptions established in Gómez and Lagakos are often assumed when designing a clinical trial. Furthermore, the set of parameters required by the ARE method corresponds to those needed for the computation of the sample size in a trial. Henceforth, neither the assumptions nor the needed anticipated values could be considered as a limitation in the design of this type of studies.

2.2 Extension of the ARE method to different copulas

Copulas can be used to define different dependence structures for pairs of random variables (Trivedi and Zimmer, 2007). In fact, multivariate distributions with similar degrees of dependence might exhibit substantially different dependence structures depending on the copula chosen. The computation of the ARE depends on the joint law between T_1 and T_2, and hence, on the copula chosen.

Given a bivariate copula C, marginal survival functions $S_1^{(j)}(t_1)$ and $S_2^{(j)}(t_2)$ of T_1 and T_2, respectively, in group j ($j = 0, 1$), and a dependence parameter θ between T_1 and T_2, the joint survival function of (T_1, T_2) is given by

$$S_{(1,2)}^{(j)}(t_1, t_2; \theta) = S_1^{(j)}(t_1) + S_2^{(j)}(t_2) - 1 + C(1 - S_1^{(j)}(t_1), 1 - S_2^{(j)}(t_2); \theta), \tag{2}$$

where C, function from I^2 to $I = [0, 1]$, is a two-dimensional copula that binds together $1 - S_1^{(j)}(t_1)$ and $1 - S_2^{(j)}(t_2)$ as follows:

$$\Pr\{T_1 \leqslant t_1, T_2 \leqslant t_2 | \text{group } j\} = C(1 - S_1^{(j)}(t_1), 1 - S_2^{(j)}(t_2); \theta).$$

Note here that the dependence parameter θ has been taken equal for both treatment groups as in Gómez and Lagakos.

The survival function of $T_* = \min\{T_1, T_2\}$, namely $S_*^{(j)}(t; \theta) = \Pr\{T_* > t; \theta | X = j\}$, for group j is given by

$$S_*^{(j)}(t; \theta) = \Pr\{T_1 > t, T_2 > t; \theta | X = j\} = S_{(1,2)}^{(j)}(t, t; \theta),$$

and can be obtained from (2) after choosing a copula. In particular, it follows that the survival, density and hazard function for the composite endpoint T_* in terms of the copulas are given by

$$S_*^{(j)}(t;\theta) = S_1^{(j)}(t) + S_2^{(j)}(t) - 1 + C(1 - S_1^{(j)}(t), 1 - S_2^{(j)}(t); \theta) \quad (3)$$

$$f_*^{(j)}(t;\theta) = f_1^{(j)}(t) + f_2^{(j)}(t) - \frac{\partial}{\partial t} C(1 - S_1^{(j)}(t), 1 - S_2^{(j)}(t); \theta) \quad (4)$$

$$\lambda_*^{(j)}(t;\theta) = \frac{f_*^{(j)}(t;\theta)}{S_*^{(j)}(t;\theta)}.$$

In our work, we extend the ARE method to the following 11 families of copulas: Frank, Gumbel, Clayton, Farlie-Gumbel-Morgenstern (FGM), Normal, t, Plackett, Galambos, Hüsler-Reiss, Tawn and t-EV. Table 1 shows the expression for each of these copulas. Since Frank, Gumbel and Clayton copulas are the copula families more often used, we present with greater detail in 4 their expressions and discuss the type of dependencies that these 3 families might exhibit, as well as the specific expression of the survival and density functions of T_*.

Table 1: Expression $C(u, v; \theta)$ and the domain of the dependence parameter θ of the following copulas: Frank, Gumbel, Clayton, Farlie-Gumbel-Morgenstern (FGM), Normal, t, Plackett, Galambos, Hüsler-Reiss, Tawn and t-EV.

Copula type	$C(u, v; \theta)$	**θ-domain**
Frank	$\frac{-1}{\theta}\log\left(1 + \frac{(e^{-\theta u}-1)(e^{-\theta v}-1)}{e^{-\theta}-1}\right)$	$(-\infty, \infty)$
Gumbel	$\exp\left(-[(-\log(u))^\theta + (-\log(v))^\theta]^{1/\theta}\right)$	$[1, \infty)$
Clayton	$\max\{[u^{-\theta} + v^{-\theta} - 1]^{-1/\theta}, 0\}$	$[-1, \infty)\backslash\{0\}$
FGM	$uv + \theta uv(1-u)(1-v)$	$[-1, 1]$
Normal	$\Phi_\theta(\Phi^{-1}(u), \Phi^{-1}(v))$	$[-1, 1]$
t	$t_{\nu,\circ}(t_\circ^{-1}(u), t_\circ^{-1}(v))$	$[-1, 1]$
Plackett	$\frac{[1+(\theta-1)(u+v)] - \sqrt{[1+(\theta-1)(u+v)]^2 - 4uv\theta(\theta-1)}}{2(\theta-1)}$	$(0, \infty)$
Galambos	$uv\exp[\{(\log(u))^{-\theta} + (\log(v))^{-\theta}\}^{-1/\theta}]$	$[0, \infty)$
Hüsler-Reiss	$\exp\{-\log(u)\Phi[\frac{1}{\theta} + \frac{1}{2}\theta\log(\frac{\log(u)}{\log(v)})] - \log(v)\Phi[\frac{1}{\theta} + \frac{1}{2}\theta\log(\frac{\log(v)}{\log(u)})]\}$	$[0, \infty)$
Tawn	$uv\exp\left(-\theta\frac{\log(u)\log(v)}{\log(uv)}\right)$	$[0, 1]$
t-EV	$\exp\left(\log(uv)A_{\theta,\nu}\frac{\log(u)}{\log(v)}\right)$	$[0, 1]$

Φ_θ and $t_{\nu,\circ}$ with ν degrees of freedom denote the standard bivariate normal and Student's t joint distribution function with correlation coefficient θ, respectively. Φ and $t_\circ$ with ν degrees of freedom denote the standard normal and Student's t distribution function, respectively. $A_{\theta,\nu}$ is the Pickands dependence function based in the bivariate Student's $t_{\nu,\circ}$. In this study, the degrees of freedom have been set to $\nu = 4$.

2.3 Computation of the ARE values using R

As seen in Section 2.1, Gómez and Lagakos relate the expression of the ARE to the following interpretable parameters: $(p_1, p_2, HR_1, HR_2, \rho, \beta_1, \beta_2)$, representing, respectively, the frequencies of observing the endpoints $\mathcal{E}_1$ and $\mathcal{E}_2$ in treatment group 0, the relative treatment effects on $\mathcal{E}_1$ and $\mathcal{E}_2$, Spearman's rank correlation between T_1 and T_2 in either group and the shape parameters of the Weibull marginal survivals.

Using the R-package `copula` (Hofert et al., 2014; Yan, 2007; Kojadinovic and Yan, 2010; Hofert and Maechler, 2011), we have written a program to compute the ARE values for a given copula chosen among the 11 families introduced in Section 2.2 (copula), taking into account whether $\mathcal{E}_1$ and $\mathcal{E}_2$ contain a terminating event (case) and as a function of the above parameters:

$$\mathrm{ARE}(\mathrm{rho}, \mathrm{beta1}, \mathrm{beta2}, \mathrm{p1}, \mathrm{p2}, \mathrm{HR1}, \mathrm{HR2}, \mathrm{case}, \mathrm{copula})$$

This function is easy to use and allows the computation of the ARE value for a large amount of simulated situations. The body of this function can be divided into three parts: (i) the first one takes care of selecting the copula that is going to be used and computes the copula dependence parameter θ for a given Spearman's correlation ρ; (ii) the second part of the algorithm builds the marginal distribution functions from the anticipated values $(p_1, p_2, HR_1, HR_2, \beta_1, \beta_2)$; and (iii) the third part of the program computes the value of the ARE for the chosen copula and the marginal distributions set in the first two parts of the function.

2.4 A case study: *Treating patients after an acute coronary syndrome with succinobucol*

A case study (Tardif et al., 2008) is used to illustrate how to use the ARE method, to show how to select the primary endpoint and to explore how sensitive are the results to the choice of a particular copula.

A randomized clinical trial (Tardif et al., 2008) was designed to test the effect of the antioxidant succinobucol on cardiovascular outcomes in patients with recent acute coronary syndrome. The primary efficacy endpoint, denoted by $\mathcal{E}_*$, was the union of $\mathcal{E}_1$ and $\mathcal{E}_2$, where $\mathcal{E}_1$ was the first occurrence between cardiovascular death, resuscitated cardiac arrest, non-fatal myocardial infarction and non-fatal stroke; and $\mathcal{E}_2$ was the first occurrence of hospitalization due to either unstable angina with objective evidence of ischaemia or coronary revascularisation. The trial did not show statistically significant differences in terms of the primary composite endpoint $\mathcal{E}_*$ obtaining a hazard ratio $HR_* = 1.00$ (95% confidence interval (CI): $0.89 - 1.13$, p-value (p)=0.96). However, secondary analysis did show a beneficial effect of succinobucol in terms of $\mathcal{E}_1$ with hazard ratio $HR_1 = 0.81$ (95% CI of $0.68 - 0.98$, p =0.029). In this trial, there were many more hospitalizations ($\mathcal{E}_2$) than $\mathcal{E}_1$ events, but, since the number of hospitalizations were similar in both treatment groups, the effect on the composite endpoint $\mathcal{E}_*$ was diluted. This is an instance of how adding an event $\mathcal{E}_2$ to a relevant one $\mathcal{E}_1$ can lead to the disappearance of the statistically significant benefit of the active treatment that would have been found on the relevant outcome ($\mathcal{E}_1$).

We examine the ARE value of the alternative treatment with succinobucol versus placebo for the reported values in the trial ($p_1 = 0.082$, $p_2 = 0.09$, $HR_1 = 0.81$) and for different values of HR_2 ranging from 0.3 to 0.95 (actual value in the trial was 1.05), for different shapes of the time-to-event distributions (nine combinations including increasing, constant and decreasing hazard functions for T_1 and T_2), for correlation values ranging from 0.15 to 0.75 and for the 11 copulas presented in Section 2.2. A total of 504 scenarios for different values of β_1, β_2, ρ and HR_2 and for fixed $p_1 = 0.082$, $p_2 = 0.09$ and $HR_1 = 0.81$ are simulated. Gómez and Lagakos use plots, such as the one given in Figure 1, to present the results and render the decision of whether to adopt a composite endpoint easier. We are using them to study the different ARE values depending on the copula chosen (Figure 2).

It is clear in this situation that the primary endpoint $\mathcal{E}_1$ would have been recommended as primary endpoint whenever $HR_2 > 0.9$ (ARE< 1). Note that actual value was $HR_2 = 1.05$. We also observe that the ARE values decrease as ρ increases, and hence, the recommendation of using $\mathcal{E}_1$ is stronger as $\mathcal{E}_1$ and $\mathcal{E}_2$ are more correlated.

Figure 2 shows that the ARE values calculated under the eleven different copulas follow the same pattern. There are 492 scenarios (97.6%) in which all copulas give the same recommendation on whether to use $\mathcal{E}_1$ or $\mathcal{E}_*$. Based on these scenarios, our conclusions summarizing the findings are the following: i) use $\mathcal{E}_*$ if $HR_2 < 0.9$ and use $\mathcal{E}_1$ if $HR_2 > 0.9$; ii) if $HR_2 = 0.9$, there are 3 scenarios in which it is more efficient to use $\mathcal{E}_*$ and 48 scenarios in which it is more efficient to use $\mathcal{E}_1$. In the remaining 12 scenarios (2.38%), listed in Table 2, there is at least one copula that gives a different recommendation than the others. All these scenarios correspond to weak correlations between T_1 and T_2 ($\rho = 0.15$ or $\rho = 0.25$) and the benefits of using the composite endpoint over the relevant endpoint are marginal (ARE values close to 1) and, as Gómez and Lagakos suggested, whenever $ARE(Z_*, Z) < 1.1$, $\mathcal{E}_1$ could be used as well as the primary endpoint.

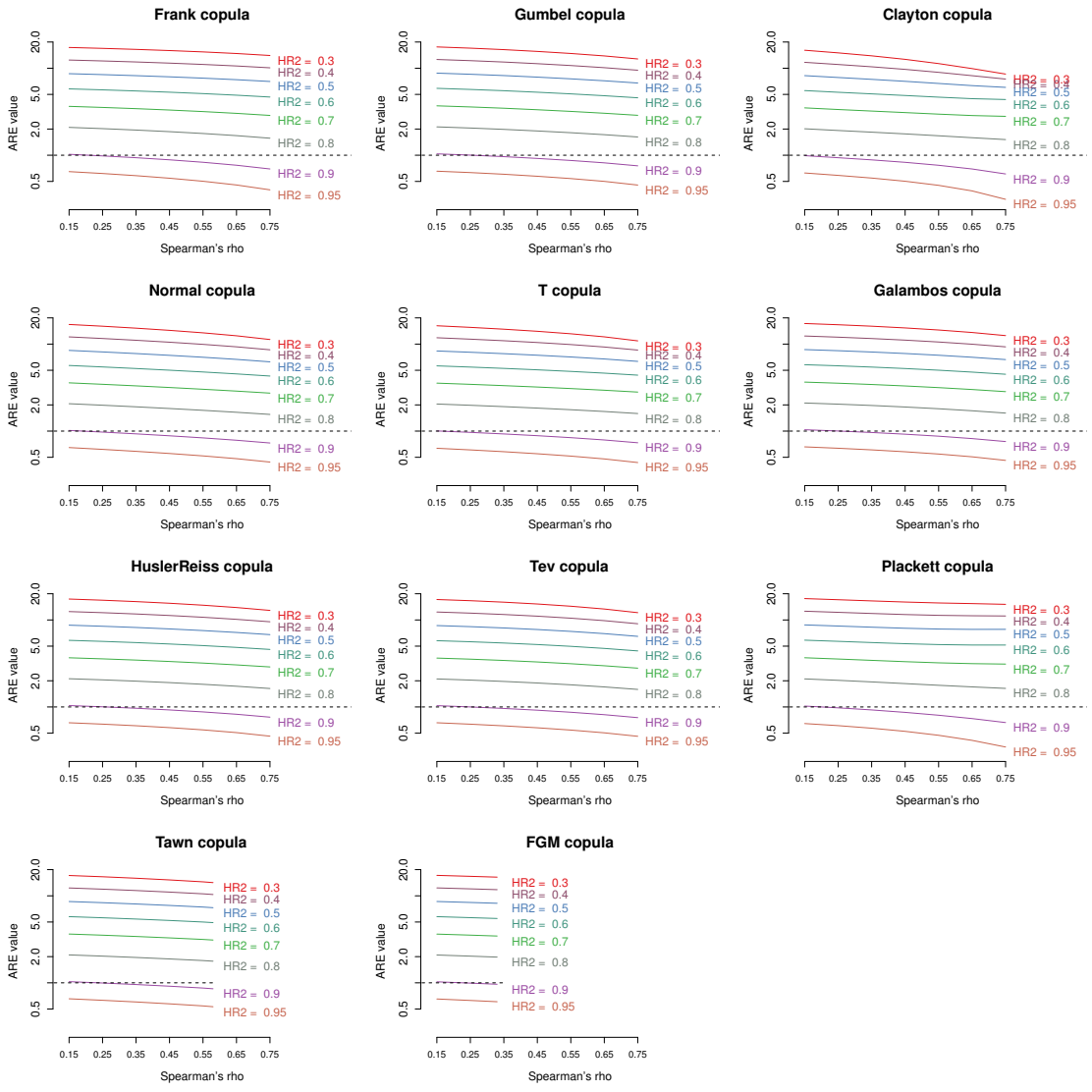

Figure 2: ARE of using logrank test based on the composite endpoint ($\mathcal{E}_*$) versus only using the relevant endpoint ($\mathcal{E}_1$) for the case study given in Section 2.4. The plots are drawn for different copulas and using values given in the study: $p_1 = 0.082$, $p_2 = 0.09$ and $HR_1 = 0.81$; for different values of HR_2 varying ρ in the abscissae and for increasing marginal hazards ($\beta_1 = \beta_2 = 2$). FGM copula only allows weak dependence ($\rho < 1/3$) and Tawn copula weak-moderate dependence ($\rho < 0.587$).

Table 2: ARE of using logrank test based on the composite endpoint (E_*) versus only using the relevant endpoint (E_1) for the case study given in Section 2.4. 12 scenarios in which at least one of the copulas give different recommendation than the others in using the composite endpoint ($p_1 = 0.082$, $p_2 = 0.09$, $HR_1 = 0.81$ and $HR_2 = 0.9$).

			ARE values depending on the copula chosen										
ρ	β_1	β_2	Frank	Gumbel	Clayton	Normal	t	Plackett	Galambos	Hüsler-Reiss	t-EV	Tawn	FGM
0.15	0.5	0.5	1.02	1.04	0.99	1.02	1.00	1.02	1.04	1.04	1.04	1.03	1.03
0.15	1	0.5	1.01	1.02	0.98	1.01	0.99	1.01	1.03	1.03	1.02	1.02	1.02
0.15	1	1	1.02	1.04	0.99	1.02	1.00	1.02	1.04	1.04	1.04	1.03	1.03
0.15	2	0.5	1.01	1.02	0.97	1.00	0.99	1.00	1.02	1.02	1.02	1.01	1.01
0.15	2	1	1.01	1.02	0.98	1.01	0.99	1.01	1.03	1.03	1.02	1.02	1.02
0.15	2	2	1.02	1.04	0.99	1.02	1.00	1.02	1.04	1.04	1.04	1.03	1.03
0.25	0.5	0.5	0.98	1.00	0.94	0.97	0.97	0.98	1.00	1.00	1.00	1.00	0.99
0.25	0.5	1	1.00	1.02	0.95	0.99	0.98	0.99	1.02	1.02	1.02	1.01	1.01
0.25	0.5	2	1.02	1.04	0.97	1.00	1.00	1.01	1.03	1.04	1.03	1.03	1.02
0.25	1	1	0.98	1.00	0.94	0.97	0.97	0.98	1.00	1.00	1.00	1.00	0.99
0.25	1	2	0.99	1.01	0.95	0.99	0.98	0.99	1.02	1.02	1.02	1.01	1.01
0.25	2	2	0.98	1.00	0.94	0.97	0.97	0.98	1.00	1.00	1.00	1.00	0.99

3 SIMULATION STUDY

We have extended the ARE method to other families of copulas in order to allow different joint behaviors between T_1 and T_2. Illustration in Figure 2 has shown that the recommendation on whether to use $\mathcal{E}_1$ or $\mathcal{E}_*$ as the primary endpoint was, almost always, the same irrespective of the copula chosen. We explore via a large simulation study how general is the pattern we have observed in this clinical trial and whether or not the choice of the copula implies fundamental changes in the recommendation based on the ARE value.

The study reproduces 145,152 situations (shown in Table 3) corresponding to:

(i) Several frequency situations for events $\mathcal{E}_1$ and $\mathcal{E}_2$ by taking probabilities p_1 and p_2 equal to 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5.

(ii) The relative treatment effect on the relevant endpoint $\mathcal{E}_1$, given by the hazard ratio HR_1, is set to 0.5, 0.6, 0.7 and 0.8, indicating that the effect of the treatment is beneficial. Each hazard ratio is combined with eight different relative treatment effects on the additional endpoint $\mathcal{E}_2$, namely HR_2, and set to 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 0.95.

(iii) Values for the shape parameters β_1 and β_2 of Weibull distribution are set to 0.5, 1 and 2 in order to have decreasing, constant and increasing hazards, respectively.

(iv) A range of associations have been considered from weak (Spearman's rank correlation $\rho = 0.15, 0.25$), through moderate ($\rho = 0.35, 0.45$) to strong ($\rho = 0.55, 0.65, 0.75$).

(v) Censoring case 1 where death is not among components of $\mathcal{E}_1$ neither among $\mathcal{E}_2$ and Censoring case 3 where death is among the components of $\mathcal{E}_1$ but not of $\mathcal{E}_2$.

Results are very similar for both censoring cases and are only presented for Case 1. A brief descriptive study of the ARE values is presented in Table 4 (72,576 simulated scenarios). ARE values for Frank, Gumbel and Clayton copulas range between 0.03 and 267.3, 0.03 and 272.7 and 0.02 and 301.3, respectively, with mean (standard deviation) equal to 4.95 (15.2), 5.08 (15.4) and 5.43 (16.9), respectively. These results are similar for other copulas.

We have compared the ARE values pairwise for any 2 copulas and for each couple the following measures of association have been evaluated: Pearson's correlation coefficient ρ, Kendall's τ and Lin's concordance correlation coefficient (CCC) (Lin, 1989; 2000). Table 5 gives these measures for the comparison of the ARE values obtained when Frank copula is used versus the ARE values obtained for any of the other 10 copulas. We observe very large coefficients for all the copulas and all the measures. In particular, Pearson's correlation coefficient ρ and Lin's concordance correlation coefficient (CCC) are

Table 3: Values of the parameters β_1, β_2, p_1, p_2, HR_1, HR_2 and ρ that yield to the configurations used to summarize the degree of agreement in adopting or not the composite endpoint depending on the choice of the copula.

β_1	0.5	1	2					
β_2	0.5	1	2					
p_1	0.05	0.1	0.2	0.3	0.4	0.5		
p_2	0.05	0.1	0.2	0.3	0.4	0.5		
HR_1	0.5	0.6	0.7	0.8				
HR_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.95
ρ	0.15	0.25	0.35	0.45	0.55	0.65	0.75	

Table 4: Descriptive analysis of the ARE value using Frank, Gumbel and Clayton copulas.

ARE using	**mean (SD)**	**min**	Q_1	**median**	Q_3	**max**
Frank copula	4.95 (15.2)	0.03	0.76	1.18	2.93	267.3
Gumbel copula	5.08 (15.4)	0.03	0.79	1.22	3.06	272.7
Clayton copula	5.43 (16.9)	0.02	0.86	1.21	3.12	301.3
Normal copula	5.13 (15.7)	0.03	0.80	1.22	3.06	280.4
t copula	5.33 (16.4)	0.03	0.84	1.24	3.13	283.2
Plackett copula	5.03 (15.5)	0.03	0.78	1.19	2.95	275.7
Galambos copula	5.08 (15.4)	0.03	0.79	1.23	3.07	272.4
Hüsler-Reiss copula	5.07 (15.4)	0.03	0.79	1.23	3.08	271.8
t-EV copula	5.08 (15.5)	0.03	0.79	1.22	3.06	273.1
Tawn copula*	5.16 (15.4)	0.06	0.81	1.29	3.21	264.1
FGM copula*	5.24 (15.2)	0.08	0.82	1.35	3.42	261.7

* Results for Tawn and FGM copulas are restricted to those scenarios in which $\rho < 0.587$ (n=51,840) and $\rho < 1/3$ (n=20,736), respectively.

above 0.99 for all the comparisons while Kendall's τ is a bit lower but above 0.92 in all the cases. Other comparisons for other pairs of copulas yielded similar results, for instance the pair Gumbel-Clayton has Pearson's ρ=0.998, Kendall's τ=0.932 and Lin's CCC=0.994.

Scatter plots for the ARE values for any 2 copulas complement the above association measures. These plots have been restricted to ARE values within the range $[0, 2]$ because an ARE value $= 1$ draws the line between recommending the relevant endpoint $\mathcal{E}_1$ or the composite endpoint $\mathcal{E}_*$. Figure 3 shows three such plots for the comparisons Frank-Gumbel, Frank-Clayton and Gumbel-Clayton. We clearly observe that the values obtained using Frank and Gumbel copulas are highly correlated, although the values are, on average, slightly larger using Gumbel copula. The ARE values for the pair Frank-Clayton are also correlated with larger variability than for the pair Frank-Gumbel. The comparison Gumbel-Clayton is also reproduced showing a similar behavior to Frank-Clayton. Comparisons to other copulas are similar to these ones and are omitted.

When it comes to the real application of the ARE method, and given the clear difficulty in having to decide between one or other copula, it is of crucial importance to know how much agreement there will be in the recommendation as a function of the copula chosen. With this in mind, we define the degree of agreement between two copulas as the percentage of situations in which both copulas agree in either recommending the use of the relevant endpoint (ARE $\leqslant 1$) or recommending the composite endpoint (ARE > 1). Based on our reproduced settings, we find a very high degree of agreement (see Table 5). In all the comparisons the degree of agreement is larger than 94%, for instance, 98.0% for the pair Frank-Gumbel, 94.7% for Frank-Clayton and 96.3% for Gumbel-Clayton.

We then study the discordant situations, that is, those scenarios yielding an ARE value with copula $C_1 > 1$ while an ARE value with copula $C_2 \leqslant 1$, which would imply a different decision on which primary endpoint to use. We restrict the results presented here to the most popular copulas: Frank, Gumbel and Clayton (see Table 6) since the comparisons with the other copulas are similar to these

Table 5: Comparison of the ARE values obtained using several families of copulas to Frank copula using Pearson's ρ, Kendall's τ, Lin's concordance correlation coefficient (CCC) and degree of agreement in recommending the main endpoint.

Copula	**Pearson's ρ**	**Kendall's τ**	**Lins's CCC**	**Agreement**
Gumbel	> 0.999	0.982	> 0.999	98.0%
Clayton	0.997	0.927	0.991	94.7%
Normal	> 0.999	0.972	0.999	97.8%
t	> 0.999	0.964	0.996	95.5%
Plackett	> 0.999	0.984	> 0.999	98.8%
Galambos	> 0.999	0.982	> 0.999	98.1%
Hüsler-Reiss	> 0.999	0.981	> 0.999	98.1%
t-EV	> 0.999	0.982	> 0.999	98.0%
Tawn*	> 0.999	0.971	> 0.999	97.4%
FGM*	> 0.999	0.997	> 0.999	99.9%

* Results for Tawn and FGM copulas are restricted to those scenarios in which $\rho < 0.587$ (n=51,840) and $\rho < {}^1/_3$ (n=20,736), respectively.

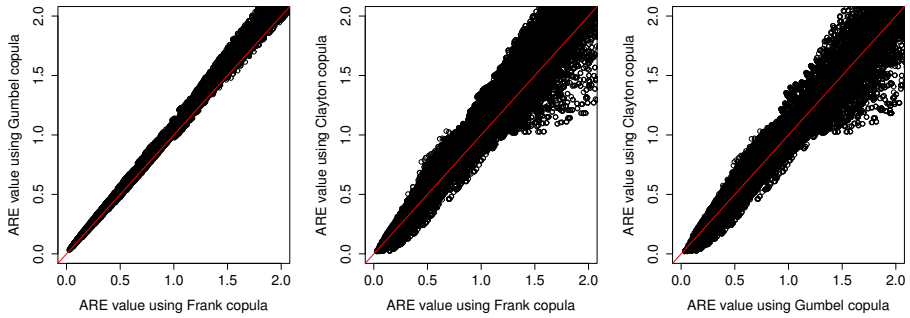

Figure 3: Scatter plot of the pairs of values using Frank and Gumbel copulas, Frank and Clayton copulas and Gumbel and Clayton copulas within the range $[0, 2]$. The line represents the situation in which both values are the same.

ones. We observe that, mostly, the difference between the two ARE values is very small (medians $\leqslant 0.09$). These situations are not worrisome because, when it comes to establishing statistical efficiency guidelines, the advantage of one endpoint over the other is very slight in the vicinity of one, and whenever $1 < \text{ARE}(Z_*, Z) < 1.1$, the benefits of using the composite endpoint over the relevant endpoint are marginal and, probably, too small to counteract the interpretational complications of a composite endpoint (Gómez and Lagakos, 2013). Furthermore, ARE values in the vicinity of 1 would imply, approximately, the same sample size whether $\mathcal{E}_1$ or $\mathcal{E}_*$ is used.

Those discordant situations where the difference is large enough so the direction of the recommendation would be reversed is lastly studied next. We first observe that the agreement between Frank and Gumbel is extremely good with absolute differences at most of 0.14. For the pairs Frank-Clayton and Gumbel-Clayton, there are respectively 1,138 (1.6%) and 617 (0.8%) discordant situations in which the distance between the two ARE values is larger than 0.15. Most of those situations (1,088 and 554, respectively) correspond to settings where the two relative treatment effects are very close ($HR_1 = HR_2$ or $HR_1 = HR_2 - 0.1$) and the relevant and the additional endpoints, T_1 and T_2, are moderate or highly correlated ($\rho \geqslant 0.35$).

We end this Section summarizing the recommendation of when to choose the composite endpoint as a function of the difference between the hazard ratios for the two endpoints, $HR_2 - HR_1$, and for the following copulas: Frank, Gumbel and Clayton. Figure 4 provides, first, the percentage of cases in which the composite endpoint should be used, and second, the percentage of cases in which there

Table 6: Descriptive analysis, when there is not agreement between copulas C_1 and C_2 (ARE $(C_1) > 1$ while ARE $(C_2) \leqslant 1$), of the absolute difference between each pair of ARE values for the pairs of copulas Frank-Gumbel, Frank-Clayton and Gumbel-Clayton.

Discordant cases	n	mean (SD)	min	Q_1	median	Q_3	P_{95}	max
$\lvert ARE_F - ARE_G \rvert$	1426	0.04 (0.03)	0.004	0.02	0.05	0.06	0.11	0.14
$\lvert ARE_F - ARE_C \rvert$	3812	0.11 (0.08)	0.001	0.04	0.09	0.17	0.27	0.36
$\lvert ARE_G - ARE_C \rvert$	2696	0.09 (0.07)	0.001	0.03	0.07	0.14	0.23	0.38

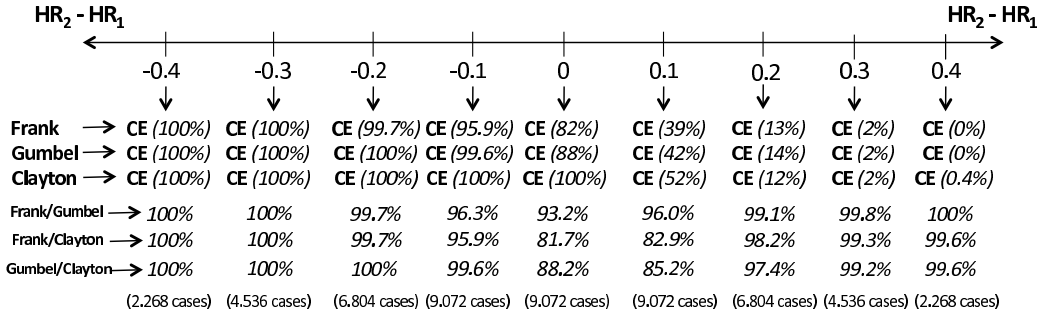

Figure 4: Percentage of situations in which the composite endpoint (CE) should be used for each copula and percentage of cases in which there is agreement between the pair of copulas depending on the difference between the hazard ratios of the relevant and the additional endpoints, HR_1 and HR_2

is agreement between the three pairs of copulas. Whenever the treatment has a larger beneficial effect on the additional endpoint $\mathcal{E}_2$ than on the relevant endpoint $\mathcal{E}_1$, the composite endpoint is almost always recommended irrespective of the copula chosen. If there is much larger beneficial effect on $\mathcal{E}_1$ than on $\mathcal{E}_2$ ($HR_2 - HR_1 \geqslant 0.3$), the recommendation of sticking to the relevant endpoint $\mathcal{E}_1$ is almost always recommended for the three copulas chosen. However, if the hazard ratios of the relevant and the additional endpoints are very close ($0 \leqslant HR_2 - HR_1 \leqslant 0.1$), the degree of agreement between Frank-Clayton and Gumbel-Clayton is in the order of 80.0%, hence the recommendation would heavily depend on the copula chosen.

4 CONCLUDING REMARKS

The decision on which endpoint to choose as the primary endpoint for the analysis of the efficacy of two treatments in a randomized clinical trial is addressed by Gómez and Lagakos (2013). Their method is based on the behavior of the Asymptotic Relative Efficiency (ARE) of the logrank test for the null hypothesis of no treatment effect observed in the composite endpoint versus the logrank test of no treatment effect observed in one of the relevant components of the composite endpoint. Once a copula has been chosen to specify the joint law between the time T_1 to the relevant endpoint $\mathcal{E}_1$ and the time T_2 to the additional $\mathcal{E}_2$ endpoint, the computation of the ARE is possible from few anticipatable parameters, such as the expected proportion of subjects experiencing the event in the control group and the hazard ratios both for the relevant $\mathcal{E}_1$ and the additional $\mathcal{E}_2$ endpoints. Plots like those shown in Figure 1 are proposed to derive recommendations without the need of anticipating the degree of association between T_1 and T_2. This paper has extended the ARE method to other families of copulas and has studied the effect that the copula has in the ARE value. The paper has as well discussed the consequences that the choice of a copula has on the recommendation for the primary endpoint.

Firstly, it has been shown that the correlation and concordance between the ARE values for the different copulas is very high, being this fact a first indication of the applicability of the ARE method. Secondly, there is a high degree of agreement between the recommendation that the different copulas would propose as to which endpoint to choose.

It has also been demonstrated that, even though the computation of the ARE strongly relies on the copula binding the marginals of T_1 and T_2, when it comes to recommending one endpoint over the other, the particular choice of the copula is, almost always, irrelevant. Cases where it matters correspond to similar values of the relative effect of treatment on the relevant and the additional endpoints (HR_1 and HR_2 very close), yielding ARE values closer to 1. In those cases, the decision on which endpoint to use has to be based on other grounds and, since the effect of the treatment is similar in the relevant and additional endpoints, the choice of the endpoint has not big implications.

Despite those few situations in which the agreement is lower, we conclude that the ARE method is robust to the choice of the copula when restricted to Frank, Gumbel, Clayton, Farlie-Gumbel-Morgenstern, Normal, t, Plackett, Galambos, Hüsler-Reiss, Tawn and t-EV families. Therefore, this methodology is widely applicable and the computation of the ARE with the purpose of choosing the primary endpoint can be, in general, restricted to one of the above given copulas.

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APPENDIX

A.1. Frank, Gumbel and Clayton copulas

The expression of Frank's copula is given by

$$C_F(u,v;\theta) = \frac{-1}{\theta}\log\left(1+\frac{(e^{-\theta u}-1)(e^{-\theta v}-1)}{e^{-\theta}-1}\right) \tag{5}$$

where the dependence parameter may assume any real value, ($\theta \in (-\infty,\infty)\backslash\{0\}$), and the limiting case $\theta \to 0$ corresponds to the independence between T_1 and T_2. Frank copula is a symmetric copula that allows both negative and positive dependence between variables and exhibits the same dependence in the left and in the right tail. A two-way scatter diagram of realizations from simulated drawings from copulas illustrates tail dependences in a bivariate framework (see Figure 5). Frank copula is best suited for applications in which tail dependence is relatively weak, as it is shown in the plot.

Gumbel copula is given by

$$C_G(u,v;\theta) = \exp\left(-[(-\log(u))^\theta + (-\log(v))^\theta]^{1/\theta}\right) \tag{6}$$

where the dependence parameter may assume any real number greater or equal than 1, ($\theta \in [1,\infty)$). Gumbel copula only allows positive dependence and exhibits relatively weak left tail dependence and strong right tail dependence (Trivedi and Zimmer, 2007) (see Figure 5). Gumbel is an appropriate choice for the joint behavior when the two endpoints are likely to simultaneously realize upper tail values.

Clayton copula is given by

$$C_C(u,v;\theta) = \max\{[u^{-\theta}+v^{-\theta}-1]^{-1/\theta},0\} \tag{7}$$

where the dependence parameter may assume any real number larger or equal than -1 ($\theta \in [-1,\infty)\backslash\{0\}$). Clayton copula only accounts for positive dependence and exhibits strong left tail dependence and relatively weak right tail dependence (Trivedi and Zimmer, 2007) (see Figure 5). Clayton copula is best suited for applications in which the two outcomes are likely to experience low values together.

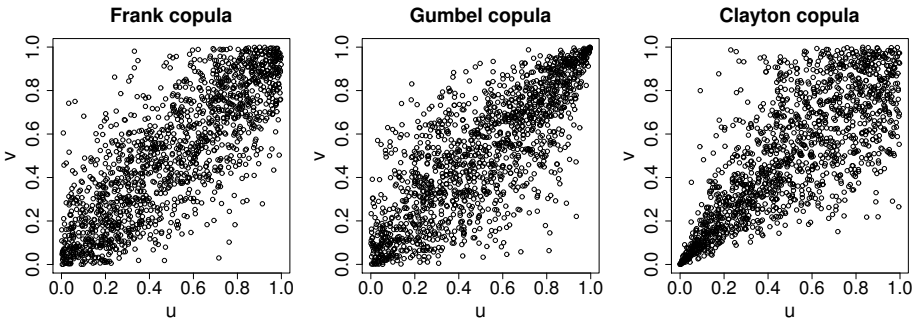

Figure 5: Simulation of 1500 samples of $C(u, v; \theta)$ using Frank, Gumbel and Clayton copulas. The dependence parameter θ has been set such that Spearman's $\rho = 0.8$ for the three copulas. The conditional distribution method (Nelsen, 1999) has been used to generate these samples.

These 3 plots in Figure 5 show how different the dependence structures might be even with similar degrees of dependence reinforcing the need of an extension of the ARE method to other families of copulas.

A.1.1. Survival and density functions of T_*

1. *Frank copula*

   If Frank copula C_F presented in (5) is used, the joint survival function for (T_1, T_2) in group j $(j = 0, 1)$ is given by

$$S^{(j)}_{(1,2)}(t_1, t_2; \theta) = \frac{-1}{\theta} \log\left(1 + \frac{(e^{-\theta S^{(j)}_1(t_1)} - 1)(e^{-\theta S^{(j)}_2(t_2)} - 1)}{e^{-\theta} - 1}\right).$$

   It follows from (4) that

$$f^{(j)}_*(t; \theta) = \frac{1}{e^{-\theta} - 1}\left[\frac{e^{-\theta S^{(j)}_1(t)}(e^{-\theta S^{(j)}_2(t)} - 1)}{e^{-\theta S^{(j)}_{(1,2)}(t,t;\theta)}} f^{(j)}_1(t) + \frac{e^{-\theta S^{(j)}_2(t)}(e^{-\theta S^{(j)}_1(t)} - 1)}{e^{-\theta S^{(j)}_{(1,2)}(t,t;\theta)}} f^{(j)}_2(t)\right].$$

2. *Gumbel copula*

   Using Gumbel copula C_G given in (6), it follows from (3) that

$$S^{(j)}_*(t; \theta) = S^{(j)}_1(t) + S^{(j)}_2(t) - 1 + \exp\left(-\left[(-\log(1 - S^{(j)}_1(t)))^\theta + (-\log(1 - S^{(j)}_2(t)))^\theta\right]^{1/\theta}\right),$$

   and from (4) that

$$f^{(j)}_*(t; \theta) = f^{(j)}_1(t) + f^{(j)}_2(t) - \exp\left(-\left[(-\log(1 - S^{(j)}_1(t)))^\theta + (-\log(1 - S^{(j)}_2(t)))^\theta\right]^{1/\theta}\right)$$
$$\left[(-\log(1 - S^{(j)}_1(t)))^\theta + (-\log(1 - S^{(j)}_2(t)))^\theta\right]^{\frac{1-\theta}{\theta}}$$
$$\left((-\log(1 - S^{(j)}_1(t)))^{\theta-1} \frac{f^{(j)}_1(t)}{1 - S^{(j)}_1(t)} + (-\log(1 - S^{(j)}_2(t)))^{\theta-1} \frac{f^{(j)}_2(t)}{1 - S^{(j)}_2(t)}\right)$$

3. *Clayton copula*

   Using Clayton copula C_C given in (7), it follows from (3) that

$$S^{(j)}_*(t; \theta) = S^{(j)}_1(t) + S^{(j)}_2(t) - 1 + [(1 - S^{(j)}_1(t))^{-\theta} + (1 - S^{(j)}_2(t))^{-\theta} - 1]^{-1/\theta}$$

and from (4) that

$$f_*^{(j)}(t;\theta) = f_1^{(j)}(t) + f_2^{(j)}(t) - [(1-S_1^{(j)}(t))^{-\theta} + (1-S_2^{(j)}(t))^{-\theta^{(j)}} - 1]^{-\frac{1+\theta}{\theta}} \left((1-S_1^{(j)}(t))^{-(1+\theta)} f_1^{(j)}(t) + (1-S_2^{(j)}(t))^{-(1+\theta)} f_2^{(j)}(t)\right)$$

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