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Some theoretical thoughts when using a composite endpoint to prove the efficacy of a treatment

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Abstract: This paper discusses, following Gómez and Lagakos (2011) methodology, to what extent is there a gain in efficiency from adding a component event to a relevant endpoint when the treatment effect on this component is not as strong as on the original relevant endpoint under ideal (independence) circumstances. It presents the bivariate copula model used to overcome the independence assumption and presents the relationship between the components of the asymptotic relative efficiency and a set of interpretable parameters.

Keywords: Asymptotic Relative Efficiency; Composite Endpoints; Composite Outcomes; Copula Model; Logrank tests

1 Introduction and motivating example

In randomized clinical trials it is common to use a composite event as endpoint and to prove the beneficial effects on treatment for this endpoint. A composite event E_* is defined as one of several events $\mathcal{E}_j$ $(j = 1, \cdots, m)$, that is, $E_* = \bigcup_{j=1}^{m} \mathcal{E}_j$. One of the reasons why scientists use composite events is to assure that, for a given sample, enough events are observed during the course of the study, being this especially crucial when one of the events is "rare" or not very frequent. The popular thinking is that "by adding" more events to the composite endpoint, we might have more power to detect treatment differences.

This problem is found in many areas but in particular in cardiovascular studies. For instance, Tardif *et al* (2008) use composite endpoints when studying the addition of succinobucol, a novel anti-oxidant and anti-inflammatory agent, to optimal medical therapy to 6,144 high-risk patients with unstable angina or who had suffered heart attacks. In the double-blind, placebo-controlled clinical trial for succinobucol the following six cardiovascular events are of interest: Cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, hospitalization due to unstable angina or hospitalization due to coronary revascularization. The study shows that succinobucol has no effect on the primary endpoint E_* where all six events are considered, while it has a beneficial effect on the composite secondary

endpoint defined as the union of the first 4 events. In this particular instance, the addition of the hospitalization events (355 (67%) in the succinobucol group and 318 (60%) in the placebo group) to the previous 4 events (207 versus 252) has yielded a non significant result for the primary E_* from a beneficial effect that the treatment has on the composite secondary endpoint.

Gómez and Lagakos' paper (2011) proposes a conceptual framework as an aid to make a decision, when planning a clinical trial, on whether to use a relevant endpoint $\mathcal{E}_1$ or the composite of $\mathcal{E}_1$ and an additional $\mathcal{E}_2$ based on prior information about the disease. The main goal of this paper is to discuss to what extent is there a gain in efficiency from adding a component event to a relevant endpoint when the treatment effect on this component is not as strong as on the original relevant endpoint under ideal (independence) circumstances, to present the copula models used to overcome the independence assumption and to frame them to derive the relative efficiency of $\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_2$ versus using just the primary endpoint $\mathcal{E}_1$.

2 Notation

We consider two-arm randomized studies involving random assignment to an active treatment ($X = 1$) or to a control treatment ($X = 0$) and we focus on the time from randomization until the first occuring of a specific set of clinical outcomes. We assume that we have two different endpoints of potential interest, $\mathcal{E}_1$ and $\mathcal{E}_2$, where each one can be either single or composite. This paper is restricted to the case where the additional event $\mathcal{E}_2$ cannot include a terminating event, such as death and it corresponds to cases 1 and 3 of Gómez and Lagakos (2011). The individuals are followed until the event of interest, or until the end of the study, whichever occurs first. Denote by $T_1^{(j)}$ and $T_2^{(j)}$ the times to $\mathcal{E}_1$ and $\mathcal{E}_2$, respectively, for patients in group $X = j$ ($j = 0, 1$) and by C the time until the end of the study (assumed equal for both groups). We assume that $T_1^{(j)}$ and $T_2^{(j)}$ are absolutely continuous so that ties cannot occur and that end-of-study censoring is the only noninformative censoring cause. We consider the composite event $\mathcal{E}_* = \mathcal{E}_1 \cup \mathcal{E}_2$ and we measure the effect of treatment on the composite endpoint $T_*^{(j)} = \min\{T_1^{(j)}, T_2^{(j)}\}$ which is the time until the occurrence of $\mathcal{E}_*$ consisting of the earlier occurring of $\mathcal{E}_1$ or $\mathcal{E}_2$.

3 Facts when the independence assumption holds

In this section we show that a beneficial effect on $\mathcal{E}_*$ can occur simultaneously with a beneficial effect on $\mathcal{E}_1$ and a harmful effect on $\mathcal{E}_2$ and that not finding a beneficial effect on the composite event $\mathcal{E}_*$ is no guarantee of not having some effect on the individual events $\mathcal{E}_1$ or $\mathcal{E}_2$.

These facts are shown for the particular case of independence between $T_1^{(j)}$ and $T_2^{(j)}$ and under the assumption that the hazards of $T_1^{(1)}$ versus $T_1^{(0)}$ ($\lambda_1^{(1)}(t)$ and $\lambda_1^{(0)}(t)$) and of $T_2^{(1)}$ versus $T_2^{(0)}$ ($\lambda_2^{(1)}(t)$ and $\lambda_2^{(0)}(t)$) are proportional. Under this assumption, the relative treatment effects on $\mathcal{E}_1$ and on $\mathcal{E}_2$ are the constant hazard ratios $\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}$ and $\frac{\lambda_2^{(1)}(t)}{\lambda_2^{(0)}(t)}$, respectively, and hazard ratios < 1 (> 1) are indicative of a beneficial (harmful) effect of the treatment.

Proposition For $j = 0, 1$, if $T_1^{(j)}$ and $T_2^{(j)}$ are independent and both $T_1^{(j)}$ and $T_2^{(j)}$ have proportional hazards, then, the hazards of $T_*^{(j)}$ ($\lambda_*^{(1)}(t)$ and $\lambda_*^{(0)}(t)$) are proportional if and only if the baseline hazard functions for the relevant and the additional endpoints, $\lambda_1^{(0)}(t)$ and $\lambda_2^{(0)}(t)$, respectively, are as well proportional. That is, if we have, for given $k_1 > k_2 > 0$, $\lambda_1^{(1)}(t) = k_1\lambda_1^{(0)}(t)$ and $\lambda_2^{(1)}(t) = k_2\lambda_2^{(0)}(t)$ for all t, then there exists k such that $\lambda_*^{(1)}(t) = k\lambda_*^{(0)}(t)$ if and only if $\lambda_2^{(0)}(t) = k_0\lambda_1^{(0)}(t)$ for all t with k and k_o related by $k = \frac{1}{1+k_0}k_1 + \frac{k_0}{1+k_0}k_2$.

Proof *Due to the independence between T_1^j and T_2^j, we have*

$$\lambda_*^{(1)}(t) = k\lambda_*^{(0)}(t) \Leftrightarrow \quad \lambda_1^{(1)}(t) + \lambda_2^{(1)}(t) = k(\lambda_1^{(0)}(t) + \lambda_2^{(0)}(t))$$

hence, since $\lambda_1^{(1)}(t) = k_1\lambda_1^{(0)}(t)$ and $\lambda_2^{(1)}(t) = k_2\lambda_2^{(0)}(t)$, it follows that

$$\begin{aligned} k_1\lambda_1^{(0)}(t) + k_2\lambda_2^{(0)}(t) &= k(\lambda_1^{(0)}(t) + \lambda_2^{(0)}(t)) \Leftrightarrow \\ (k_1 - k)\lambda_1^{(0)}(t) &= (k - k_2)\lambda_2^{(0)}(t) \Leftrightarrow \quad \lambda_2^{(0)}(t) = \frac{(k_1 - k)}{(k - k_2)}\lambda_1^{(0)}(t). \end{aligned}$$

This result establishes that if the baseline hazard functions, $\lambda_1^{(0)}(t)$ and $\lambda_2^{(0)}(t)$ are proportional, then the hazard ratio $\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}$ is a linear combination of $\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}$ and $\frac{\lambda_2^{(1)}(t)}{\lambda_2^{(0)}(t)}$, and this has several relevant implications which we summarize in the next Corollary.

Corollary Under the assumptions of the proposition and assuming that $\lambda_2^{(0)}(t) = k_0\lambda_1^{(0)}(t)$,

1. If treatment has no effect on $\mathcal{E}_1$ neither on $\mathcal{E}_2$ ($k_1 = k_2 = 1$), then treatment has no effect on $\mathcal{E}_*$ ($k = 1$).

2. The effect that treatment has on $\mathcal{E}_*$ lies always between the effects that the treatment has on $\mathcal{E}_1$ and $\mathcal{E}_2$. That is, if $k_1 = \frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)} < \frac{\lambda_2^{(1)}(t)}{\lambda_2^{(0)}(t)} = k_2$ then $k_1 < \frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)} < k_2$ and hence: i) if the treatment effect is

beneficial on $\mathcal{E}_1$ and $\mathcal{E}_2$ ($k_1 < k_2 \leq 1$), the treatment will prove to be beneficial on $\mathcal{E}_*$ and ii) if the treatment effect is harmful on $\mathcal{E}_1$ and $\mathcal{E}_2$ ($1 \leq k_1 < k_2$), the treatment will prove to be harmful on $\mathcal{E}_*$. Analogously if $k_1 > k_2$.

3. If treatment has a beneficial effect for $\mathcal{E}_1$ ($k_1 < 1$) and a harmful effect for $\mathcal{E}_2$ ($k_2 > 1$), you can choose k_0 conveniently to prove either no effect or a beneficial or harmful effect on $\mathcal{E}_*$. For instance, taking $k_1 = 0.5$ and $k_2 = 2$, i) if $k_0 = 1.5$ we have $k = 2$ and treatment has a harmful effect for $\mathcal{E}_*$, ii) if $k_0 = 0.5$ then $k = 1$ and treatment has no effect on $\mathcal{E}_*$ and iii) if $k_0 = 0.25$ then $k = 0.8$ and treatment has a beneficial effect for $\mathcal{E}_*$.

4 Using copulas to model the bivariate survival function

So far we have proved that under the ideal situation of two independent endpoints the beneficial effect on a composite endpoint does not imply the beneficial effect in either component. However, most of the times the two endpoints are correlated and the hazard of the composite cannot be decomposed as the sum of the two marginal hazards. In this situation the joint law of $T_1^{(j)}$ and $T_2^{(j)}$ is needed and we face the challenge of modelling an empirical problem in such a way that is not too complex but still realistic. We can model the joint dependence structure by means of a copula function. A copula is best described, as in Joe (1997), as a multivariate distribution function that is used to bind each marginal distribution function to form the joint. The copula parameterises the dependence between the margins, while the parameters of each marginal distribution function can be estimated separately. The approach via copulas allows much more general types of dependencies to be included than would usually be invoked by a conceptual approach. The approach to formulating a multivariate distribution using a copula is based on the idea that a simple transformation can be made of each marginal variable in such a way that each transformed marginal variable has a uniform distribution. Once this is done, the dependence structure can be expressed as a multivariate distribution on the obtained uniforms, and a copula is precisely a multivariate distribution on uniform random variables. There are many families of copulas which differ in the detail of the dependence they represent. A family will typically have several parameters which relate to the strength and form of the dependence.
Among several classes of copulas the Archimedean copulas are an important family, which have a simple form with properties such as associativity, symmetry and have a variety of dependence structures (Trivedi and Zimmer, 2007). One particularly simple form of an Archimedean bidimensional

copula is given by

$$H(t_1, t_2) = \varphi^{-1}\left(\sum_{i=1}^{2} \varphi(F_i(t_i))\right)$$

where φ is a generator function satisfying $\varphi(1) = 0$, $\lim_{t\to 0} \varphi(t) = \infty$, $\varphi'(t) < 0$ and $\varphi''(t) > 0$, and where F_i $(i = 1, 2)$ are univariate marginal probability distribution functions.

Different choices of the generator function yield as well different copulas with specific features. We are basing our computations in Frank copula's generator defined as $\varphi(t) = -\ln\left(\frac{e^{-\theta t}-1}{e^{-\theta}-1}\right)$ for dependence parameter θ, $-\infty < \theta < \infty$, because it has the following useful features: it permits negative dependence between the marginals, the dependence is symmetric in both tails, it is comprehensive, that is, it might represent perfect negative dependence, independence and perfect positive dependence between variates. Furthermore, Spearman's ρ linear correlation between $F_1(T_1^{(j)})$ and $F_2(T_2^{(j)})$ is given by $\rho = \rho(\theta) = 1 - \frac{12}{\theta}[\frac{1}{\theta}\int_0^\theta \frac{t}{e^t-1} - \frac{2}{\theta^2}\int_0^\theta \frac{t^2}{e^t-1}dt]$ holding a 1-1 relationship between ρ and θ.

For every group $j = 0, 1$ and given marginal survival (density) functions $S_1^{(j)}(t_1)$ and $S_2^{(j)}(t_2)$ $(f_1^{(j)}(t_1)$ and $f_2^{(j)}(t_2))$ for $T_1^{(j)}$ and $T_2^{(j)}$ and given equal association parameter θ between $T_1^{(j)}$ and $T_2^{(j)}$, the joint survival and density functions based on Frank's copula are as follows:

$$\begin{aligned} S^{(j)}(t_1, t_2; \theta) &= -\theta^{-1}\log\left\{1 + \frac{(e^{-\theta S_1^{(j)}(t_1)} - 1)(e^{-\theta S_2^{(j)}(t_2)} - 1)}{e^{-\theta} - 1}\right\} \\ f_{(1,2)}^{(j)}(t_1, t_2; \theta) &= \frac{\theta e^{-\theta(S_1^{(j)}(t_1)+S_2^{(j)}(t_2)))}}{e^{-2\theta S^{(j)}(t_1,t_2;\theta)}(e^{-\theta}-1)}[f_1^{(j)}(t_1)][f_2^{(j)}(t_2))] \qquad (1) \end{aligned}$$

For $j = 0, 1$, the survival and density function of $T_*^{(j)} = \min\{T_1^{(j)}, T_2^{(j)}\}$ become equal to

$$\begin{aligned} S_*^{(j)}(t; \theta) &= S^{(j)}(t_1, t_2; \theta) \qquad (2) \\ f_*^{(j)}(t) &= \frac{e^{-\theta S_1^{(j)}(t)}(e^{-\theta S_2^{(j)}(t)} - 1)}{e^{-\theta S_*^{(j)}(t;\theta)}(e^{-\theta} - 1)} f_1^{(j)}(t) + \frac{e^{-\theta S_2^{(j)}(t)}(e^{-\theta S_1^{(j)}(t)} - 1)}{e^{-\theta S_*^{(j)}(t;\theta)}(e^{-\theta} - 1)} f_2^{(j)}(t) \end{aligned}$$

if Frank's copula is used.

5 Log rank test and Asymptotic Relative Efficiency

For the two-arm randomized study described in Section 2, we assume that we have two independent samples, that end-of-study censoring is the only noninformative censoring cause, that end-of-study censoring is identical

across groups and that treatment groups have proportional hazards. To check whether treatment has a beneficial effect, we might use endpoint $\mathcal{E}_1$ carrying the relevant information of the disease process or we might add endpoint $\mathcal{E}_2$ and use the composite $\mathcal{E}_*$. The null hypothesis of no treatment difference is given either by $H_0 : \lambda_1^{(0)}(\cdot) = \lambda_1^{(1)}(\cdot)$ in terms of the marginal hazards of $T_1^{(0)}$ and $T_1^{(1)}$ if $\mathcal{E}_1$ is being used or by $H_0 : \lambda_*^{(0)}(\cdot) = \lambda_*^{(1)}(\cdot)$ in terms of the marginal hazards of $T_*^{(0)}$ and $T_*^{(1)}$ when inferences would be based on $\mathcal{E}_*$. In both cases the logrank test Z (and Z_*) is the chosen statistic on which to base the conclusions.

Following Gómez and Lagakos (2011) we base the strategy in the behaviour of the asymptotic relative efficiency (ARE) of Z_* versus Z given by

$$\mathrm{ARE}(Z_*, Z) = \frac{\left(\int_0^1 \log\left(\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}\right) f_*^{(0)}(t)dt\right)^2}{\left(\log\left(\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}\right)\right)^2 (\int_0^1 f_*^{(0)}(t)dt)(\int_0^1 f_1^{(0)}(t)dt)} \tag{3}$$

where $f_1^{(0)}(t)$ and $f_*^{(0)}(t)$ are, respectively, the densities for $T_1^{(0)}$ and $T_*^{(0)}$ in group 0. The method proposes to use the composite endpoint instead of the primary endpoint if $\mathrm{ARE}(Z_*, Z) > 1.25$, to stick to the primary endpoint if $\mathrm{ARE}(Z_*, Z) < 1.1$, and whenever $1.1 < \mathrm{ARE}(Z_*, Z) < 1.25$ balance the benefits of using the composite endpoint over the relevant endpoint on the particular setting.

If such a method is being used for the design of a given clinical trial, the computation of the $\mathrm{ARE}(Z_*, Z)$ would need to be based on easily interpretable parameters such as 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 $\mathrm{HR}_1 = \frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}$ and $\mathrm{HR}_2 = \frac{\lambda_2^{(1)}(t)}{\lambda_2^{(0)}(t)}$ and to a lesser extent by the dependence degree between the relevant endpoint $T_1^{(0)}$ and the additional endpoint $T_2^{(0)}$ given by Spearman's rank correlation coefficient ρ.

As we see in (3) the $\mathrm{ARE}(Z_*, Z)$ depends on the marginal laws of $T_1^{(0)}$ and $T_*^{(0)}$ in group 0 and on the hazard ratios $\frac{\lambda_1^{(1)}(t)}{\lambda_1^{(0)}(t)}$ and $\frac{\lambda_*^{(1)}(t)}{\lambda_*^{(0)}(t)}$. Assuming Frank's copula for both groups with equal association parameter θ, the density of $T_*^{(j)}$ in group j $(j = 0, 1)$ is given by (2). Hence to derive the $\mathrm{ARE}(Z_*, Z)$ in terms of the above listed interpretable parameters we have to specify marginal parametric laws for $T_1^{(j)}$ and $T_2^{(j)}$ for both treatment groups 0 and 1 and we have to relate their parameters to the frequencies p_1 and p_2, the hazard ratios HR_1 and HR_2 and the Spearman's coefficient ρ.

If for $j = 0, 1$ and $k = 1, 2$, we choose Weibull distributions with scale parameters $b_k^{(j)}$ and shape parameters β_k chosen equal for both groups so

that the proportionality of the hazards holds, the marginal survival function is given by $S_k^{(j)}(t) = \exp\left(-(t/b_k^{(j)})^{\beta_k}\right)$. Then the relationship between $(b_1^{(0)}, b_2^{(0)}, b_1^{(1)}, b_2^{(1)}, \beta_1, \beta_2, \rho)$ and $(p_1, p_2, \mathrm{HR}_1, \mathrm{HR}_2, \beta_1, \beta_2, \rho)$ is given by:

1. The scale parameter $b_1^{(0)}$ is a function of p_1 and β_1 given by $b_1^{(0)} = \frac{1}{(-\log(1-p_1))^{1/\beta_1}}$.
2. (a) If $\mathcal{E}_1$ does not include a terminating event, the scale parameter $b_2^{(0)}$ is a function of p_2 and β_2 given by $b_2^{(0)} = \frac{1}{(-\log(1-p_2))^{1/\beta_2}}$.

   (b) If $\mathcal{E}_1$ includes a terminating event, $T_2^{(j)}$ might be censored by $T_1^{(j)}$ and the probability of observing $\mathcal{E}_2$ will depend on whether $T_1^{(j)} \leq T_2^{(j)}$ or not and hence on the joint density $f_{(1,2)}^{(0)}(t_1, t_2; \theta)$ given in (1). In this case, the scale parameter $b_2^{(0)}$ is a function of $(p_1, p_2, \rho, \beta_1, \beta_2)$ and it is found as the solution of equation $p_2 = \int_0^1 \int_v^\infty f_{(1,2)}^{(0)}(u, v; \theta) du dv$, or equivalently $p_2 = \int_{VL}^1 \left(\int_0^{UL^{(0)}(y)} g(x, y) dx\right) dy$ where $UL^{(0)}(y) = S_1^{(0)}((-\log y)^{1/\beta_2} b_2^{(0)})$, $VL = S_2^{(0)}(1)$ and $g(x, y) = \frac{\theta(1-e^{-\theta})\exp\{-\theta(x+y)\}}{(e^{-\theta}+e^{-\theta(x+y)}-e^{-\theta x}-e^{-\theta y})^2}$.
3. For $k = 1, 2$, the scale parameter $b_k^{(1)}$ is function of the scale parameter $b_k^{(0)}$, the shape parameter β_k and the hazard ratio HR_k as follows: $b_k^{(1)} = \frac{b_k^{(0)}}{\mathrm{HR}_k^{\frac{1}{\beta_k}}}$

Based on the guidelines established in Gómez and Lagakos (2011) they prove that often adding an endpoint to a relevant endpoint can be helpful if the relative effect on treatment on the additional endpoint is larger than on the relevant endpoint, harmful if the effect is smaller and whenever the effect on both endpoints is about the same the frequency of observing the endpoints and their correlation have to be taken into account before reaching a decision.

6 Illustration and conclusion

When studying the addition of succinobucol (Tardif *et al*, 2008) we can split the six components composite event $\mathcal{E}_*$ (cardiovascular death, resuscitated cardiac arrest, non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization) into the relevant endpoint $\mathcal{E}_1$ formed by cardiovascular death, resuscitated cardiac arrest, non-fatal myocardial infarction and non-fatal stroke and the additional endpoint $\mathcal{E}_2$ formed by hospitalization for unstable angina and coronary revascularization in order

to assess the best choice as primary endpoint for the analysis under the circumstances of this randomized clinical trial. Based on the published parameters the frequencies of observing $\mathcal{E}_1$ and $\mathcal{E}_2$ are respectively $p_1 = 0.0822$ and $p_2 = 0.0903$ with relative treatment effect on $\mathcal{E}_1$ given by a hazard ratio of $\mathrm{HR}_1 = 0.81$ and on $\mathcal{E}_2$ given by $\mathrm{HR}_2 = 1.05$. For these values the $\mathrm{ARE}(Z_*, Z)$ lies between 0.05 and 0.18 for all the possible degrees of association between $T_1^{(j)}$ and $T_2^{(j)}$ and irrespective of the chosen values for the shape parameters. It is hence clear in this case that adding hospitalization for unstable angina and coronary revascularization is not recommended. As a matter of fact the trial failed to show a statistically significant difference on $\mathcal{E}_*$ (p-value = 0.955) between the succinobucol group and the control group, while it showed a beneficial effect of succinobucol on the relevant endpoint $\mathcal{E}_1$ (p-value = 0.029). Note here that as pointed out in Section 3 composing an event on which treatment has a beneficial effect with an event showing no significant effect we have produced a composite endpoint where the effect has vanished. This clinical trial is extensively discussed in Gómez, Dafni and Gómez (2011) who assess, within the cardiovascular research context, the characteristics of the candidate individual endpoints that should govern the choice of using a composite endpoint as the primary endpoint by means of the asymptotic relative efficiency.
The paper has given more insight into the relationship between the hazard ratios of $T_k^{(1)}$ versus $T_k^{(0)}$ $(k = 1, 2)$ and of $T_*^{(1)}$ versus $T_*^{(0)}$ and has provided a straightforward relationship between the components of the $\mathrm{ARE}(Z_*, Z)$ and a small set of interpretable parameters.

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References

Gómez, G. and Lagakos, S.W. (2011). Statistical Considerations when Using a Composite Endpoint for Comparing Treatment Groups. *Submitted.*

Gómez, G. , Dafni, U. and Gómez, M. (2011). Informed Choice of Composite Endpoints in Cardiovascular Trials. *Submitted.*

Joe, H. (1997). *Multivariate Models and Dependence Concepts.* London: Chapman and Hall.

Tardif, J-C., McMurray, J.J.V., Klug, E. *et al.* (2008). Effects of succinobucol (AGI-1067) after an acute coronary syndrome: a randomised, double-blind, placebo-controlled trial. *The Lancet*, **371**, 1761-1768.

Trivedi, P.K. and Zimmer, D.M. (2005). Copula Modeling: An Introduction for Practitioners. *Foundations and Trends in Econom.*, **1**, 1-111.