Online Supplemental Appendix Material

Application of the Wei-Lachin Multivariate One-Sided Test to Multiple Event-time Outcomes

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A. The Composite Analysis Hazard Rate

Lachin [7] describes a simulation model using two exponential distributions with a shared frailty that induces a correlation between the event times for the two outdcomes. In the simulation model, in the ith group, three random independent exponential event times are generated as

$$\begin{aligned} t_1 &\sim exponential(\lambda_{ia} - \lambda_{iF}) \\ t_2 &\sim exponential(\lambda_{ib} - \lambda_{iF}) \\ t_3 &\sim exponential(\lambda_{iF}) \end{aligned} \tag{1}$$

where $0 < \lambda_{iF} < min\,[\lambda_{ia}, \lambda_{ib}]$. Correlated event times are then obtained as

$$\begin{aligned} t_{ia} &= \min(t_1, t_3) \sim exponential(\lambda_{ia}) \\ t_{ib} &= \min(t_2, t_3) \sim exponential(\lambda_{ib}). \end{aligned} \tag{2}$$

Under this structure the hazard of the individual events equals the desired marginal hazard λ_{ij} since the hazard function of the minimum of two independent exponential variables is the sum of the respective hazards. The common frailty (t_3) induces a correlation among the event times (t_{ia}, t_{ib}) and determines the corresponding probability that both events occur in the same subject.

The composite outcome then consists of the time to the first component event, designated as $t_{im} = \min(t_{ia}, t_{ib}) \sim exponential(\lambda_{im})$. Since $\min(t_{ia}, t_{ib}) = \min(t_1, t_2, t_3)$ then the composite even hazard rate is $\lambda_{im} = \lambda_{ia} + \lambda_{ib} - \lambda_{iF}$. This quantity can be used to to compute sample size or power for a composite analysis of multiple correlated event times.

It is also of interest to note that the resulting hazard ratio for the composite outcome under this model is

$$HR_m = \frac{\lambda_{Ea} + \lambda_{Eb} - \lambda_{EF}}{\lambda_{Ca} + \lambda_{Cb} - \lambda_{CF}} = \frac{(HR_a \times \lambda_{Ca}) + (HR_b \times \lambda_{Cb}) - \lambda_{EF}}{\lambda_{Ca} + \lambda_{Cb} - \lambda_{CF}}$$

that is a function of the hazard rates and hazard ratios as well as the frailties that determine the correlation among the event times in each group. Conversely, the Wei-Lachin test is based on the average log hazard ratios for the component events that do not depend on the frailty.

B. Simulations

Appendix Figure 1 describes the power of the Wei-Lachin test versus the composite analysis from 2,000 simulations of $n = 100$ subjects per group using the above bivariate exponential model. The Wei-Lachin test was computed using separate Cox PH models with the Wei-Lin-Weissfeld covariance matrix, and the composite analysis employed the logrank test, both at $\alpha = 0.05$ one-sided.

The power of the two approaches was evaluated over a range of group differences (namely hazard ratios for the two individual outcomes HR_a and HR_b), and for various combinations of hazard rates in the control group (λ_{Ca} and λ_{Cb}). The simulations employed a hazard rate for frailty of $\lambda_F = 0.05$ and an additional independent right censoring time with hazard rate $\lambda_c = 0.05$, the same in the two groups, with no administrative censoring.

Figure 1.A shows power as a function of a range of hazard ratios for the two outcomes (HR_a, HR_b) and equal hazards for the two outcomes in the control group $(\lambda_{Ca}, \lambda_{Cb}) = (0.20, 0.20)$. The top pair of curves apply to the case where treatment has a very strong beneficial effect on the first outcome

$HR_a = 0.5$. When treatment also has a strong effect on the second outcome ($HR_b < 0.7$) the two tests have similar power, but as the latter effect approaches the null then the power of the Wei-Lachin test is increasingly greater. For a moderate treatment effect on the first outcome, typical of that used to power many trials ($HR_a = 0.75$), the Wei-Lachin test has greater power over the range of values for the effect on the other outcome (HR_b ranging from 0.5 to 1). When treatment has no effect on the first outcome ($HR_a = 1$), the Wei-Lachin test also has greater power than the composite analysis over the range of values for HR_b.

Figure 1.B describes power when the hazard rates for the outcomes differ, $(\lambda_{Ca}, \lambda_{Cb}) = (0.25, 0.125)$. In this case, if treatment has a strong effect on the more prevalent outcome ($HR_a = 0.5$) and also on the less prevalent outcome ($HR_b < 0.8$) then the two tests have equivalent power, but as the hazard ratio for the less prevalent outcome (HR_b) approaches the null then the composite test has greater power. For a moderate treatment effect on the more prevalent outcome ($HR_a = 0.75$), the Wei-Lachin has greater power when there is also an effect on the other outcome, HR_b ranging from 0.5 to 0.8, but lesser power as the latter approaches the null. When treatment has no effect on the more prevalent outcome ($HR_a = 1$), the Wei-Lachin test also has greater power than the composite provided that treatment also has some effect on the less prevalent outcome.

C. Joint covariance matrix of treatment group coefficient estimates.

Using the developments in Pipper et al. [8], Appendix Table 1 presents the treatment group coefficients from multiple Cox PH models that were fit to the component events within each composite outcome, and the joint covariance matrix of the group coefficients for all outcomes. These were provided by the *mmm* function in the **R** package *multcomp*.

Figure 1: **Comparison of the power of the Wei-Lachin test and the standard time-to-the-first event (Composite) over a range of hazard ratios with $n = 100$ per group at $\alpha = 0.05$ one-sided. A:** $(\lambda_{Ca}, \lambda_{Cb}) = (0.20, 0.20)$**, B:** $(\lambda_{Ca}, \lambda_{Cb}) = (0.25, 0.125)$**.**

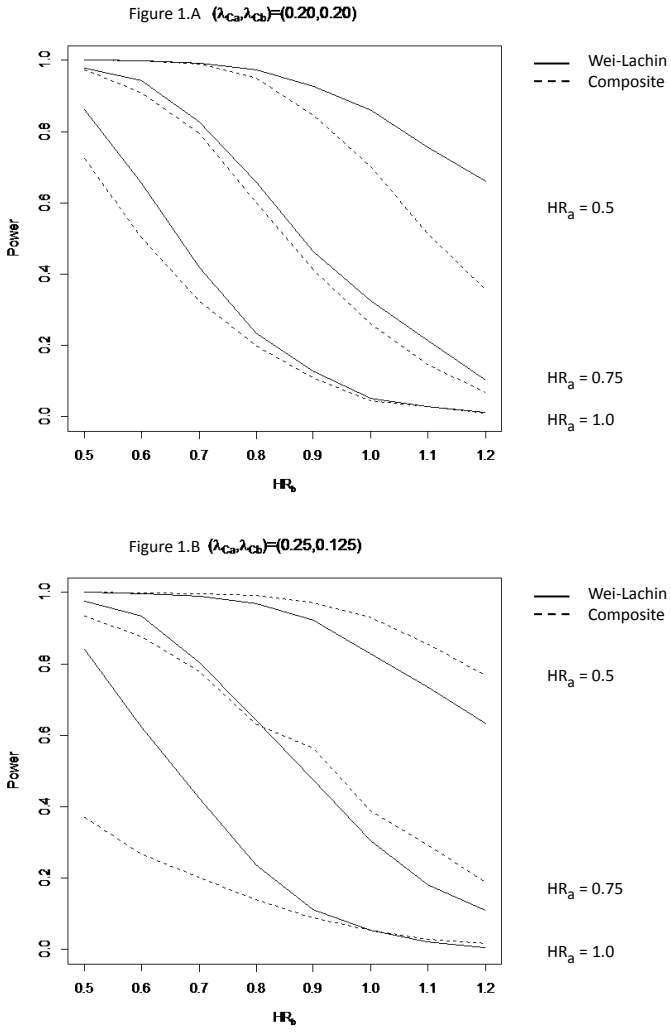

Table 1: **The treatment group coefficients from separate models for each outcome, and the joint covariance matrix obtained from the information sandwich.**

Outcome	$\widehat{\beta}$	CV death	MI	Revasc.	Stroke	CHF
1. CV death	-0.05001	0.013429	0.001100303	0.000387448	-0.000259	0.002705
2. Non-fatal MI	-0.00056	0.001100	0.009050159	0.001461058	0.000666	0.002102
3. Revascularization	-0.02281	0.000387	0.001461058	0.002691985	0.000198	0.000554
4. Non-fatal stroke	-0.32252	-0.000259	0.000666042	0.000198074	0.031516	0.001331
5. CHF	-0.25748	0.002705	0.002101913	0.000554073	0.001331	0.016987