Web-based Supplementary Materials for Nonparametric Group Sequential Methods for Recurrent and Terminal Events from Multiple Follow-up Windows

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1 Appendix A: Asymptotic Multivariate Distribution of $\tilde{\mathscr{T}}_k = \left\{\tilde{\mathscr{T}}_1(s_1), \ldots, \tilde{\mathscr{T}}_k(s$ $k = 1, \ldots, K$

In this section, we prove that the multivariate distribution of $\tilde{\mathscr{T}}_k = \left\{\tilde{\mathscr{T}}_1(s_1), \ldots, \tilde{\mathscr{T}}_k(s_k)\right\}$ is a mean zero Normal distribution with covariance matrix Σ_k for $k = 1, \ldots, K$ as described in the main text of the manuscript.

We start from our unstandardized test statistic at analysis time s:

$$\mathscr{T}(s) = \sqrt{\frac{n_1(s)n_2(s)}{n_1(s)+n_2(s)}}\{\hat{\mu}_1(s,\tau) - \hat{\mu}_2(s,\tau)\},$$

which can be written as

$$\mathscr{T}(s) = \sqrt{\frac{n_2(s)}{n_1(s)+n_2(s)}}\sqrt{n_1(s)}\hat{\mu}_1(s,\tau) - \sqrt{\frac{n_1(s)}{n_1(s)+n_2(s)}}\sqrt{n_2(s)}\hat{\mu}_2(s,\tau), \tag{1}$$

where $n_g(s)/\{n_1(s)+n_2(s)\} \xrightarrow{p} \pi_g(s)$. Suppose at analysis time s, combining information of the time to first event captured in all b follow-up windows of length τ, we record M unique event times $\{0 \equiv T_0 < T_1 < ... < T_M < T_{M+1} \equiv \tau\}$. Then, by Taylor series expansion,

$$\sqrt{n_g(s)}\hat{\mu}_g(s,\tau) = \sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1} - T_m)exp\left\{-\sum_{j=0}^{m}\frac{dN_g(s,T_j)}{Y_g(s,T_j)}\right\}$$

is asymptotically equivalent in distribution to:

$$\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)\,exp\left\{-\sum_{j=0}^{m}\lambda_g^W(s,T_j)dT_j\right\} \tag{2}$$

$$+\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)\left[\sum_{j=0}^{m}-exp\left\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\right\}\frac{dN_g(s,T_j)}{Y_g(s,T_j)}\right] \tag{3}$$

$$-\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)\left[\sum_{j=0}^{m}-exp\left\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\right\}\lambda_g^W(s,T_j)dT_j\right] \tag{4}$$

$$+\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)\frac{1}{2!}exp\left\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\right\}\left[\sum_{j=0}^{m}\left\{\frac{dN_g(s,T_j)}{Y_g(s,T_j)}-\lambda_g^W(s,T_j)dT_j\right\}\right]^2 \tag{5}$$

$$+\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)[\text{higher order terms}] \tag{6}$$

Terms (5) and (6) converge to zero in probability using similar arguments to those shown in Tayob and Murray (2014) Appendix A. When terms (2) and (4) are combined into the test statistic, $\mathscr{T}(s)$, under the null hypothesis, they cancel with terms from the other treatment group. Hence, the asymptotic behavior of $\mathscr{T}(s)$ is based on term (3) for groups $g = 1, 2$, which can be further rewritten as

$$\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)\left[\sum_{j=0}^{m}-exp\left\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\right\}\frac{dN_g(s,T_j)}{Y_g(s,T_j)}\right]$$

$$= -\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)exp\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\}\sum_{j=0}^{m}\frac{dN_g(s,T_j)}{Y_g(s,T_j)},$$

By Taylor series expansion, this term is asymptotically equivalent in distribution to

$$-\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)exp\left\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\right\}\times$$

$$\left\{\sum_{j=0}^{m}\frac{EdN_g(s,T_j)}{EY_g(s,T_j)}\right. \tag{7}$$

$$+\sum_{j=0}^{m}\left[\frac{1}{EY_g(s,T_j)}[dN_g(s,T_j)-EdN_g(s,T_j)]-\frac{EdN_g(s,T_j)}{EY_g(s,T_j)^2}[Y_g(s,T_j)-EY_g(s,T_j)]\right] \tag{8}$$

$$\left.+[\text{higher order terms}]\right\}. \tag{9}$$

Using arguments similar to those given in Tayob and Murray (2014), the higher order terms in (9) converge to zero in probability. When term (7) appears in $\mathscr{T}(s)$, it cancels with its corresponding term from the other treatment group under the null hypothesis. Hence, the asymptotic behavior of $\mathscr{T}(s)$ is based on term (8) which upon noting that $EdN_g(s,T_j)/EY_g(s,T_j) = \lambda_g^W(s,T_j)$ and $EY_g(s,T_j) = \sum_{l=1}^{b} Pr(X_{gi}(s,t_l) \geq T_j)$ can be algebraically rearranged as:

$$-\sqrt{n_g(s)}\sum_{m=0}^{M}(T_{m+1}-T_m)exp\left\{-\sum_{j'=0}^{m}\lambda_g^W(s,T_{j'})dT_{j'}\right\}\sum_{j=0}^{m}\frac{dN_g(s,T_j)-Y_g(s,T_j)\lambda_g^W(s,T_j)}{\sum_{l=1}^{b} Pr(X_{gi}(s,t_l)\geq T_j)}$$

or in more standard stochastic integral notation as:

$$-\sqrt{n_g(s)}\int_0^{\tau} exp\left\{-\int_0^{u_2}\lambda_g^W(s,u_1)du_1\right\}\int_0^{u_2}\frac{dN_g(s,u_1)-Y_g(s,u_1)\lambda_g^W(s,u_1)}{\sum_{l=1}^{b} Pr(X_{gi}(s,t_l)\geq u_1)}du_2. \tag{10}$$

Summarizing the above remarks,

$$\mathscr{T}(s) = \sqrt{\frac{n_2(s)}{n_1(s)+n_2(s)}}\sqrt{n_1(s)}\hat{\mu}_1(s,\tau) - \sqrt{\frac{n_1(s)}{n_1(s)+n_2(s)}}\sqrt{n_2(s)}\hat{\mu}_2(s,\tau)$$

is asymptotically equivalent in distribution to

$$\sqrt{\pi_1(s)}\sqrt{n_2(s)}\int_0^{\tau} exp\left\{-\int_0^{u_2}\lambda_2^W(s,u_1)du_1\right\}\int_0^{u_2}\frac{dN_2(s,u_1)-Y_2(s,u_1)\lambda_2^W(s,u_1)}{\sum_{l=1}^{b} Pr(X_{2i}(s,t_l)\geq u_1)}du_2$$

$$-\sqrt{\pi_2(s)}\sqrt{n_1(s)}\int_0^{\tau} exp\left\{-\int_0^{u_2}\lambda_1^W(s,u_1)du_1\right\}\int_0^{u_2}\frac{dN_1(s,u_1)-Y_1(s,u_1)\lambda_1^W(s,u_1)}{\sum_{l=1}^{b} Pr(X_{1i}(s,t_l)\geq u_1)}du_2. \tag{11}$$

Recall that

$$N_g(s,u) = \sum_{i=1}^{n_g(s)} N_{gi}(s,u) = \sum_{i=1}^{n_g(s)}\sum_{j=1}^{b} N_{gi}(s,t_j,u)$$

and

$$Y_g(s,u) = \sum_{i=1}^{n_g(s)} Y_{gi}(s,u) = \sum_{i=1}^{n_g(s)}\sum_{j=1}^{b} Y_{gi}(s,t_j,u).$$

We define:

$$Z_{ij}\{\hat{\mu}_g(s,\tau)\} = \int_0^{\tau} exp\left\{-\int_0^{u_2}\lambda_g^W(s,u_1)du_1\right\}\int_0^{u_2}\frac{dN_{gi}(s,t_j,u_1)-Y_{gi}(s,t_j,u_1)\lambda_g^W(s,u_1)du_1}{\sum_{l=1}^{b} Pr\{X_{gi}(s,t_l)\geq u_1\}}du_2$$

and

$$Z_i\{\hat{\mu}_g(s,\tau)\} = \sum_{j=1}^{b} Z_{ij}\{\hat{\mu}_g(s,\tau)\}.$$

We can write equation (11) as

$$\mathscr{T}^*(s) = \sqrt{\pi_1(s)}\sqrt{n_2(s)}\frac{\sum_{i=1}^{n_2(s)} Z_i\{\hat{\mu}_2(s,\tau)\}}{n_2(s)} - \sqrt{\pi_2(s)}\sqrt{n_1(s)}\frac{\sum_{i=1}^{n_1(s)} Z_i\{\hat{\mu}_1(s,\tau)\}}{n_1(s)}. \tag{12}$$

Note that $Z_i\{\hat{\mu}_g(s,\tau)\}$ only depends on patient i and is independent and identically distributed for $i = 1, \ldots, n_g(s)$. As a result, the multivariate central limit theorem can be used to determine the asymptotic joint distribution of $\{\mathscr{T}^*(s_1), \ldots, \mathscr{T}^*(s_k)\}, k = 1, \ldots, K$, when each statistic is formulated as in equation (12). As a result, the covariance matrix of $\{\mathscr{T}^*(s_1), \ldots, \mathscr{T}^*(s_k)\}$ with component $Cov\{\mathscr{T}^*(s_{k_1}), \mathscr{T}^*(s_{k_2})\}$, can be estimated using empirical covariances of $Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}$ and $Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}$, for $g = 1, 2$, where appropriate, as follows.

First, without loss of generality, assume $s_{k_1} \le s_{k_2}$ so that $n_g(s_{k_1}) \le n_g(s_{k_2})$ with $n_g(s_{k_1})$ patients contributing (correlated) data from both analysis times. Then

$$Cov\{\mathscr{T}^*(s_{k_1}), \mathscr{T}^*(s_{k_2})\}$$

$$= \sum_{g=1}^{2} Cov\left[\sqrt{\pi_{3-g}(s_{k_1})}\sqrt{n_g(s_{k_1})}\frac{\sum_{i=1}^{n_g(s_{k_1})} Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}}{n_g(s_{k_1})}, \sqrt{\pi_{3-g}(s_{k_2})}\sqrt{n_g(s_{k_2})}\frac{\sum_{i=1}^{n_g(s_{k_2})} Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}}{n_g(s_{k_2})}\right].$$

$$= \sum_{g=1}^{2} \sqrt{\pi_{3-g}(s_{k_1})}\sqrt{\pi_{3-g}(s_{k_2})}\frac{n_g(s_{k_1})}{\sqrt{n_g(s_{k_1})n_g(s_{k_2})}} Cov\left[Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}, Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}\right],$$

which is asymptotically equivalent to

$$= \sum_{g=1}^{2} \sqrt{\pi_{3-g}(s_{k_1})\pi_{3-g}(s_{k_2})\psi_g(s_{k_1},s_{k_2})}\, Cov\left[Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}, Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}\right],$$

where for group $g = 1, 2$, $\psi_g(s_{k_1}, s_{k_2})$ is the limiting proportion of patients entered at s_{k_1} of those eventually entered by s_{k_2}, that is estimated by $n_g(s_{k_1})/n_g(s_{k_2})$. Therefore, we can estimate $Cov\left[Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}, Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}\right]$ with the empirical covariance of sample realizations of $Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}$ and $Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}$, that is,

$$\widehat{Cov}\left[Z_i\{\hat{\mu}_g(s_{k_1},\tau)\}, Z_i\{\hat{\mu}_g(s_{k_2},\tau)\}\right] = \sum_{i=1}^{n_g(s_{k_1})} \frac{[z_i\{\hat{\mu}_g(s_{k_1},\tau)\} - \bar{z}\{\hat{\mu}_g(s_{k_1},\tau)\}][z_i\{\hat{\mu}_g(s_{k_2},\tau)\} - \bar{z}\{\hat{\mu}_g(s_{k_2},\tau)\}]}{n_g(s_{k_1}) - 1}.$$

where $z_i\{\hat{\mu}_g(s,\tau)\}$ and $\bar{z}\{\hat{\mu}_g(s,\tau)\}$ are defined in terms of $z_{ij}\{\hat{\mu}_g(s,\tau)\}$ in main manuscript Section 3. However, this estimation can be improved upon by updating $z_{ij}\{\hat{\mu}_g(s_{k_1},\tau)\}$ with quantities that that do not depend on analysis time and thus can be estimated better using the full data at the later analysis time s_{k_2}. In particular, since both $dN_{gi}(s_{k_1}, t_j, u_1)/Y_{gi}(s_{k_1}, t_j, u_1)$ and $dN_{gi}(s_{k_2}, t_j, u_1)/Y_{gi}(s_{k_2}, t_j, u_1)$ estimate

$\lambda_{gi}(t_j, u_1)du_1$, and the latter term uses more data, we replace $dN_{gi}(s_{k_1}, t_j, u_1)$ with

$$Y_{gi}(s_{k_1}, t_j, u_1)\frac{dN_{gi}(s_{k_2}, t_j, u_1)}{Y_{gi}(s_{k_2}, t_j, u_1)}.$$

Similarly, we replace $Y_g(s_{k_1}, u_1)/n_g(s_{k_1})$, which is an estimate of $\sum_{l=1}^{b} Pr\{T_{gi}(s_{k_1}, t_l) \geq u_1\}Pr\{C_{gi}(s_{k_1}, t_l) \geq u_1\}$, with

$$\left[\sum_{i=1}^{n_g(s_{k_2})} \frac{I\{T_{gi} \geq u_1 + t_l\}}{n_g(s_{k_2})}\right]\left[\sum_{i=1}^{n_g(s_{k_1})} \frac{I\{C_{gi}(s_{k_1}) \geq u_1 + t_l\}}{n_g(s_{k_1})}\right].$$

Here, terms involving the event time are estimated using updated data, while terms involving the censoring distribution remain relevant to analysis time s_{k_1}. Putting these modifications together gives us

$$\begin{aligned}\tilde{z}_{ij}\{\hat{\mu}_g(s_{k_1}, \tau)\} = \int_0^{\tau} exp\{-\int_0^{u_2}\frac{dN_g(s_{k_1}, u_1)}{Y_g(s_{k_1}, u_1)}\}\Bigg[\int_0^{u_2} \\ \left\{\sum_{l=1}^{b}\left(\sum_{i=1}^{n_g(s_{k_2})} I\{T_{gi} \geq u_1 + t_l\}\sum_{i\prime=1}^{n_g(s_{k_1})} I\{C_{gi\prime}(s_{k_1}) \geq u_1 + t_l\}\right)\right\}^{-1} \\ \times\, n_g(s_{k_1})n_g(s_{k_2})Y_{gi}(s_{k_1}, t_j, u_1)\left\{\frac{dN_{gi}(s_{k_2}, t_j, u_1)}{Y_{gi}(s_{k_2}, t_j, u_1)} - \frac{dN_g(s_{k_1}, u_1)}{Y_g(s_{k_1}, u_1)}\right\}\Bigg]du_2.\end{aligned}$$

as an updated version of $z_{ij}\{\hat{\mu}_g(s_{k_1}, \tau)\}$ for use in covariance terms. So that we replace the $z_{ij}\{\hat{\mu}_g(s_{k_1}, \tau)\}$ terms in $z_i\{\hat{\mu}_g(s_{k_1}, \tau)\}$ and $\bar{z}\{\hat{\mu}_g(s_{k_1}, \tau)\}$ with $\tilde{z}_{ij}\{\hat{\mu}_g(s_{k_1}, \tau)\}$ to obtain $\tilde{z}_i\{\hat{\mu}_g(s_{k_1}, \tau)\}$ and $\bar{\tilde{z}}\{\hat{\mu}_g(s_{k_1}, \tau)\}$. And we update the empirical covariance as

$$\widehat{Cov}\left[Z_i\{\hat{\mu}_g(s_{k_1}, \tau)\}, Z_i\{\hat{\mu}_g(s_{k_2}, \tau)\}\right] = \sum_{i=1}^{n_g(s_{k_1})} \frac{[\tilde{z}_i\{\hat{\mu}_g(s_{k_1}, \tau)\} - \bar{\tilde{z}}\{\hat{\mu}_g(s_{k_1}, \tau)\}][z_i\{\hat{\mu}_g(s_{k_2}, \tau)\} - \bar{z}\{\hat{\mu}_g(s_{k_2}, \tau)\}]}{n_g(s_{k_1}) - 1}.$$

For the standardized version of test statistic, $\tilde{\mathscr{T}}(s_k), s_k = s_1, \ldots, s_K$, we work with the corresponding standardized form of the more tractible random variable that is asymptotically equivalent in distribution, namely,

$$\frac{\mathscr{T}^*(s_k)}{\sqrt{\pi_2(s_k)\sigma_1^2(s_k) + \pi_1(s_k)\sigma_2^2(s_k)}}.$$

which also gives $\tilde{\mathscr{T}}_k$ an asymptotic mean zero multivariate Normal distribution with covariance matrix Σ_k. Because the test statistic is standardized to have variance 1.0. We only need to estimate the off-diagonal elements $\sigma_{k_1k_2}$ via

$$\hat{\sigma}_{k_1k_2} = \frac{\widehat{Cov}\left\{\mathscr{T}^*(s_{k_1}), \mathscr{T}^*(s_{k_2})\right\}}{\sqrt{\hat{\pi}_2(s_{k_1})\tilde{\sigma}_1^2(s_{k_1}) + \hat{\pi}_1(s_{k_1})\hat{\sigma}_2^2(s_{k_1})}\sqrt{\hat{\pi}_2(s_{k_2})\tilde{\sigma}_1^2(s_{k_2}) + \hat{\pi}_1(s_{k_2})\hat{\sigma}_2^2(s_{k_2})}}. \tag{13}$$

Section 3 in the main manuscript gives estimates $\hat{\pi}_g(s_k)$ for $s_k = s_{k_1}, s_{k_2}$ and $\hat{\sigma}_g^2(s_{k_2})$ using the most up-to-date information. Estimate $\tilde{\sigma}_g^2(s_{k_1})$ in equation (13) for $g = 1, 2$ is modified by replacing $z_{ij}\{\hat{\mu}_g(s_{k_1}, \tau)\}$ with $\tilde{z}_{ij}\{\hat{\mu}_g(s_{k_1}, \tau)\}$. Therefore, we have

$$
\begin{aligned}
\hat{\sigma}_{k_1 k_2} =& \{\hat{\pi}_2(s_{k_1})\tilde{\sigma}_1^2(s_{k_1}) + \hat{\pi}_1(s_{k_1})\tilde{\sigma}_2^2(s_{k_1})\}^{-\frac{1}{2}} \{\hat{\pi}_2(s_{k_2})\hat{\sigma}_1^2(s_{k_2}) + \hat{\pi}_1(s_{k_2})\hat{\sigma}_2^2(s_{k_2})\}^{-\frac{1}{2}} \\
& \times \sum_{g=1}^{2} \sqrt{\hat{\pi}_{3-g}(s_{k_1})\hat{\pi}_{3-g}(s_{k_2})\hat{\psi}_g(s_{k_1}, s_{k_2})} \Bigg(\sum_{i=1}^{n_g(s_{k_1})} \{n_g(s_{k_1}) - 1\}^{-1} \\
& \times [\tilde{z}_i\{\hat{\mu}_g(s_{k_1}, \tau)\} - \bar{\tilde{z}}\{\hat{\mu}_g(s_{k_1}, \tau)\}] [z_i\{\hat{\mu}_g(s_{k_2}, \tau)\} - \bar{z}\{\hat{\mu}_g(s_{k_2}, \tau)\}] \Bigg).
\end{aligned} \tag{14}
$$

2 Appendix B: Simulated Cumulative Power in the Special Case with Independent Recurrent and Terminal Event Distributions

Figure S1 shows simulated power for the group sequentially monitored CL, TM and LR statistics when all events within each individual are statistically independent, but otherwise have marginal distributions as given in section 5 of the main manuscript. The CL statistic (triangles) had the highest power in this special case, followed closely by the TM statistic (circles) and distantly by the LR method(+).

3 Appendix C: Additional Simulation Results

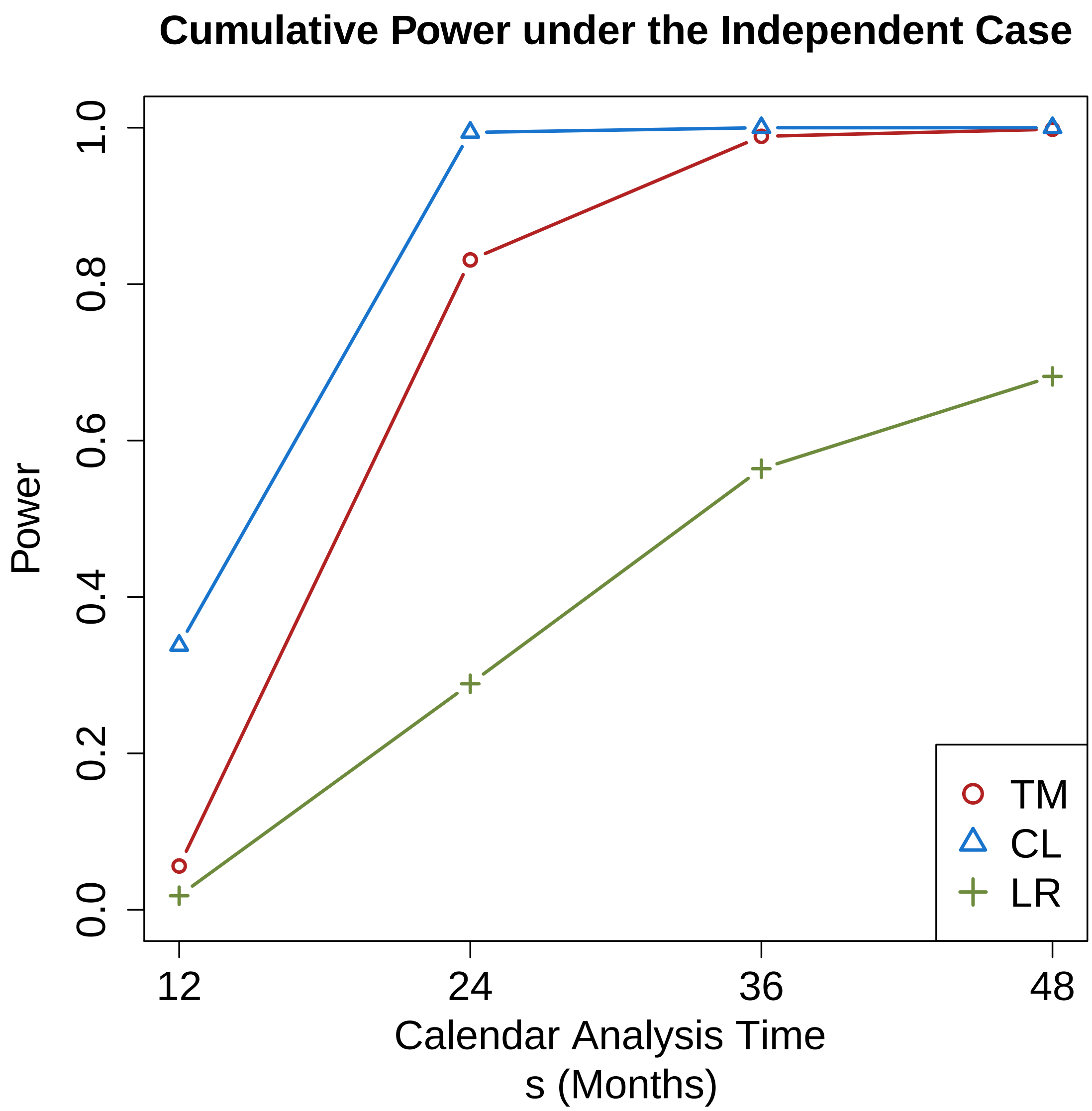

Figure S1: Simulated Cumulative Power in the Special Case with Independent Recurrent and Terminal Event Distributions (TM: Tayob and Murray (2014) test; CL: Cook and Lawless (1996) test; LR: log-rank test.)

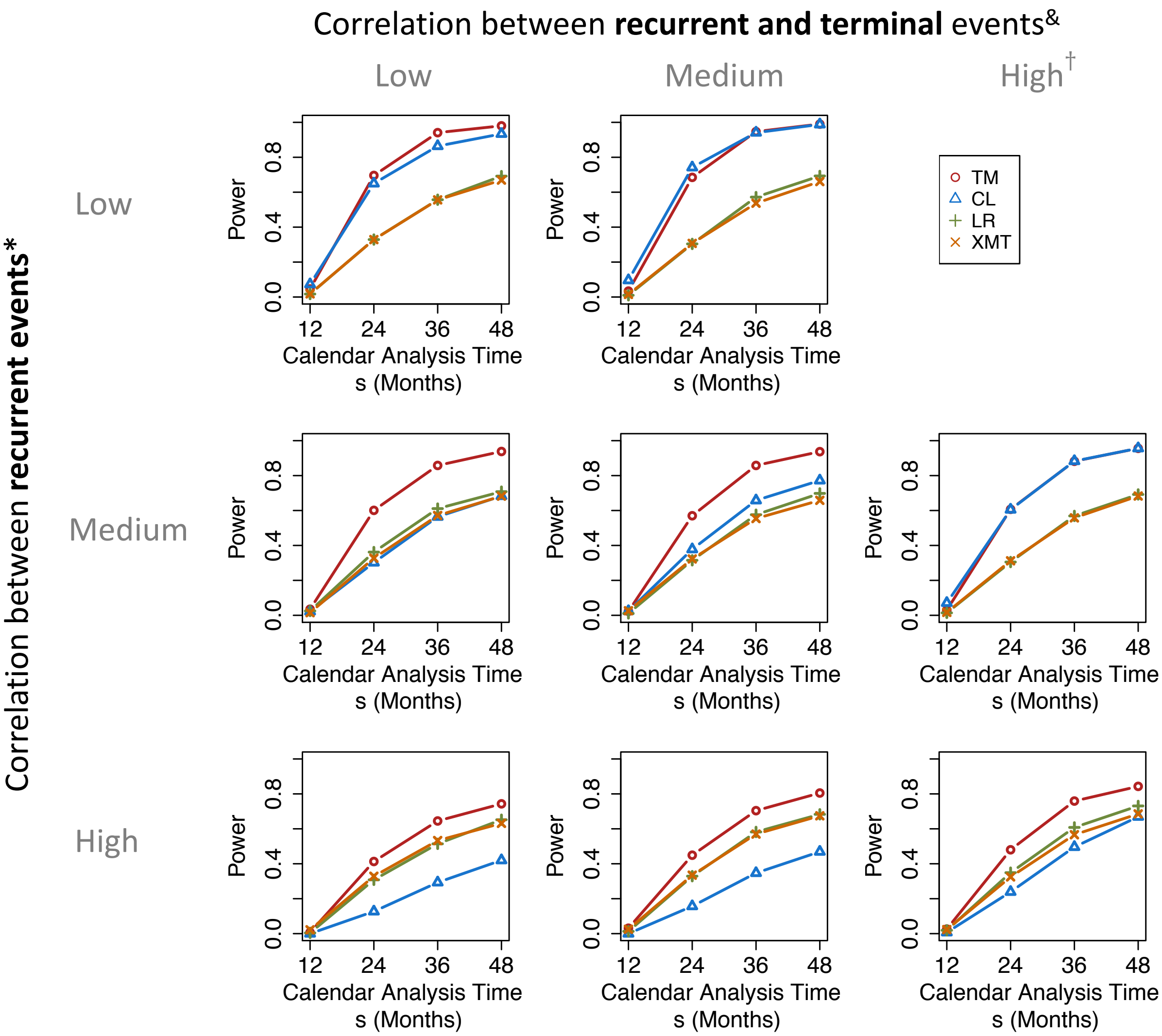

Figure S2: Cumulative Power at Each Analysis Time by Varying Levels of Correlation between Recurrent Events (Rows) and Correlation between Recurrent and Terminal Events (Columns).
(TM: Tayob and Murray (2014) test; CL: Cook and Lawless (1996) test; LR: log-rank test; XMT: Xia, Murray and Tayob (2018).)

† Data is not shown for the case with low ρ_1 and high ρ_2 since this covariance structure was difficult to construct. Intuitively, it is difficult to have gap times weakly correlated with one another and at the same time all highly correlated with the terminal event time.

* Low, medium to high correlations between recurrent events are generated from $\rho_1 = 0.3, 0.5$ and 0.7, respectively.

& Low, median to high correlations between recurrent and terminal events are generated from $\rho_2 = 0.3, 0.5$ and 0.7, respectively.

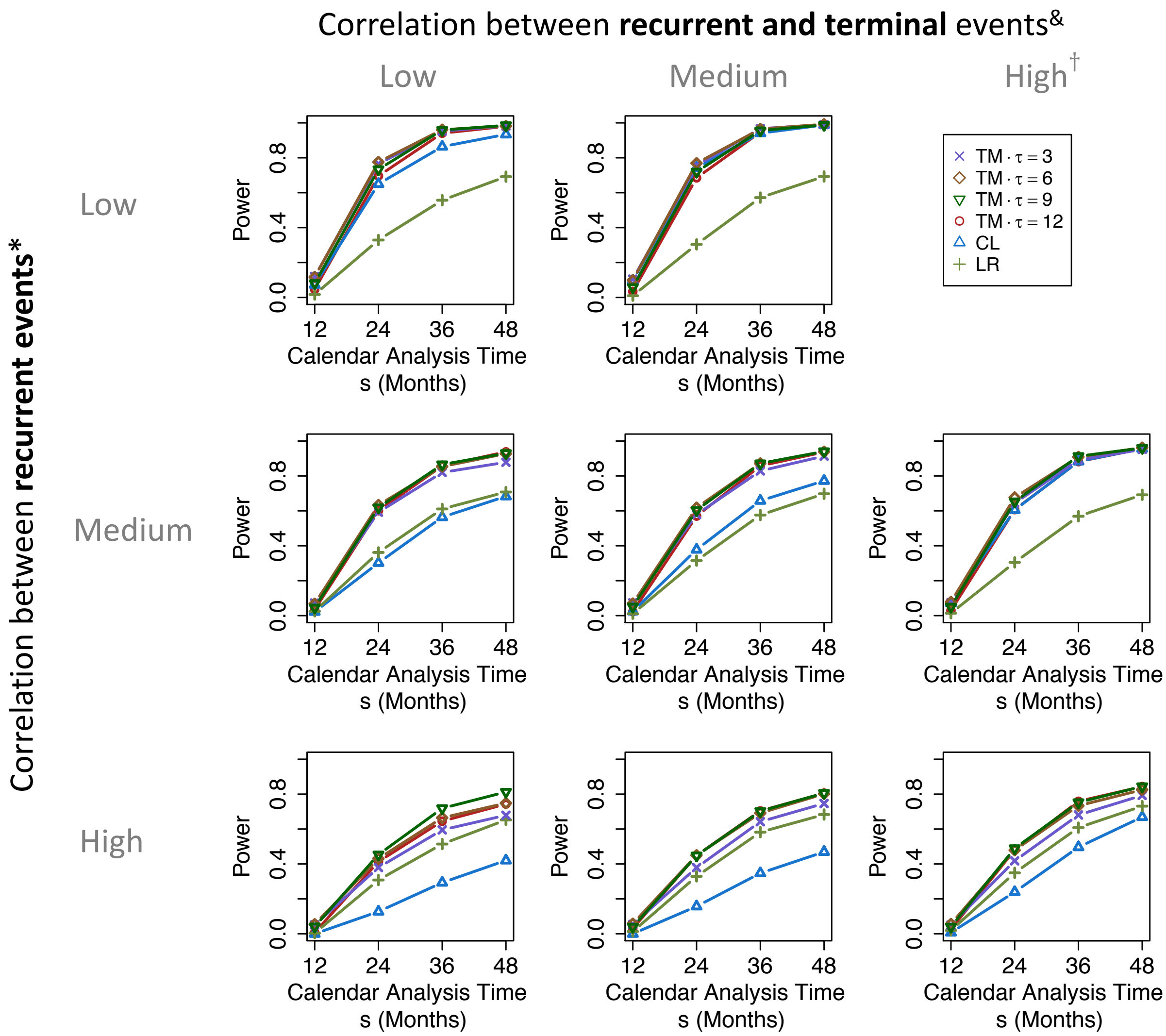

Figure S3: Cumulative Power at Each Analysis Time by Varying Levels of Correlation between Recurrent Events (Rows) and Correlation between Recurrent and Terminal Events (Columns).
(TM: Tayob and Murray (2014) test; CL: Cook and Lawless (1996) test; LR: log-rank test.)
† Data is not shown for the case with low ρ_1 and high ρ_2 since this covariance structure was difficult to construct. Intuitively, it is difficult to have gap times weakly correlated with one another and at the same time all highly correlated with the terminal event time.
* Low, medium to high correlations between recurrent events are generated from $\rho_1 = 0.3, 0.5$ and 0.7, respectively.
& Low, median to high correlations between recurrent and terminal events are generated from $\rho_2 = 0.3, 0.5$ and 0.7, respectively.