# Supplementary Material for "Sample Size Formulae for Two-Stage Randomized Trials with Censored Data"

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## 1 Sample Size Formulae for More General Two-Stage Randomized Trials

In the simple two-stage sequential multiple assignment randomized trial considered in the paper, nonresponders to both first-stage treatments are rerandomized to one of two second-stage treatments, while responders are not rerandomized. In practice, all kinds of variants of two-stage designs exist. For example, in a two-stage sequential multiple assignment randomized trial that is currently underway for drug addicted pregnant women conducted by Hendree Jones at the RTI International, Research Triangle Park, North Carolina, USA, both responders and and nonresponders to the first stage of treatment are rerandomized. At first, all subjects are randomized to either a traditional reinforcement based treatment or a reduced reinforcement based treatment with reduced intensity/scope. Response to the initial treatment is assessed at week 2. The criterion for nonresponse involved adherence to treatment as well as positive urine tests. Early non-responders are rerandomized to receive either the same treatment or a greater intensity/scope of their initial treatment, while responders are randomized to either the same intensity of treatment or a decreased intensity or scope of the initial treatment. An interesting outcome in this trial is time until dropout from counseling. In another trial concerning the treatment of children with autism conducted by Connie Kasari at the University of California at Los Angels, only nonresponders to one of the two first-stage treatments are rerandomized. In this trial, all subjects are initially randomized to either joint attention/joint engagement supplemented with an individualized augmentative/alternative communication system, or joint attention/joint engagement and spoken communication intervention, both treatments lasting for 12 weeks. At the end of the 12 week period, response is assessed, using measures such as the number of words and the number of communicative functions used spontaneously during parent-child interaction. All responders stay on the initial treatment; nonresponders to joint attention/joint engagement supplemented with an individualized augmentative/alternative communication system start more intense treatment, and only nonresponders to joint attention/joint engagement and spoken communication intervention are further randomized to two options: start more intense treatment or switch to joint attention/joint engagement supplemented with an individualized augmentative/alternative communication system. The primary outcome of this trial is not a failure time outcome, but the time until the number of words used spontaneously during parent-child interaction reaches a certain level could also be of interest.

The approach developed in our paper for sample size calculation can be generalized to the following general two-stage sequential multiple assignment randomized trials. Denote $A_1$ to be the coding variable for the options for the first-stage treatment, which can take values $1, 2, \cdots$, or $k_1$. Responders to $A_1 = j$ are further randomized to one of the second-stage treatments $A_{2j}^R = 1, 2, \cdots$, or $k_{2j}^R$, and nonresponders to $A_1 = j$ are further randomized to one of the second-stage treatments $A_{2j}^N = 1, 2, \cdots$, or $k_{2j}^N$, for $j = 1, 2, \cdots, k_1$. The two-stage sequential multiple assignment randomized trial considered in the paper corresponds to the special case in which $k_1 = 2$, $k_{21}^N = k_{22}^N = 2$ and $k_{21}^R = k_{22}^R = 1$. The test statistic based on the weighted Kaplan–Meier estimator and the weighted log rank test statistic for comparing two treatment strategies can be defined in a similar manner as before; only the weights need to be modified. See the following for examples. Further, it is easy to see that in the more general designs, the asymptotic variance formulae in Theorems 1 and 3 given below in Section 2 remain unchanged, but with a different formula for the weight functions. The different weight functions results in different upper bounds on the variances and hence different sample size formulae. In the following we illustrate this with two examples.

First consider a design in which both responders and nonresponders are rerandomized, as in the trial for drug dependent pregnant women. Suppose all subjects are first randomized to treatment $A_1 = j$ with probability $p_{1j}$, $j = 1, 2, \cdots, k_1$. Those who respond to $A_1 = j$ are further randomized to $A_{2j}^R = i$ with probability $p_{2j}^{Ri}$, and those who do not respond to $A_1 = j$ are further randomized to $A_{2j}^N = i$ with probability $p_{2j}^{Ni}$. Consider the following two strategies: strategy 111, assign treatment $A_1 = 1$ as the initial treatment, and if there is response then assign $A_{21}^R = 1$ but if there is no response, then assign $A_{21}^N = 1$, and strategy 222, assign $A_1 = 2$ first, and responders to $A_1 = 2$ are then assigned $A_{22}^R = 2$ and nonresponders to $A_1 = 2$ are assigned $A_{22}^N = 2$. Let $R$ be the indicator for observing a response. If we use the notation in the paper, then $R = I\{S > \min(T, C)\}$, where $S$ is time to nonresponse, $T$ is the failure time, and $C$ is the censoring time. In some trials a criterion for response instead of nonresponse is defined. In that case, if we denote $S^*$ to be time to response, then the definition of $R$ should be changed to $R = I\{S^* \leq \min(T, C)\}$. Using this notation, the time independent weight function for strategy 111 is

$$W_1 = \frac{I(A_1 = 1)}{p_{11}} \left\{ \frac{RI(A_{21}^R = 1)}{p_{21}^{R1}} + \frac{(1 - R)I(A_{21}^N = 1)}{p_{21}^{N1}} \right\},$$

and the weight function for strategy 222 is

$$W_2 = \frac{I(A_1 = 2)}{p_{12}} \left\{ \frac{RI(A_{22}^R = 2)}{p_{22}^{R2}} + \frac{(1-R)I(A_{22}^N = 2)}{p_{22}^{N2}} \right\}.$$

If we use the test based on the weighted Kaplan-Meier with time independent weights to calculate the sample size, we need upper bounds for

$$E\left[\int_0^\tau \frac{W_j}{\bar{F}_j(u)\bar{F}_C(u)}\{dN(u) - Y(u)d\Lambda_j(u)\}\right]^2,\ j = 1, 2,$$

where $\bar{F}_j(t)$ and $\Lambda_j(t)$ are the survival function and cumulative hazard function of $T_j$ — the potential failure time under strategy $jjj$, $j = 1, 2$. Denote the counting process and the at risk process of $T_j$ by $N_j(t)$ and $Y_j(t)$, respectively, for $j = 1, 2$. By repeated expectations, we have, when $j = 1$,

$$\begin{aligned}
& E\left[\int_0^\tau \frac{W_1}{\bar{F}_1(u)\bar{F}_C(u)}\{dN(u) - Y(u)d\Lambda_1(u)\}\right]^2 \\
= \;& EW_1^2 \left[\int_0^\tau \frac{1}{\bar{F}_1(u)\bar{F}_C(u)}\{dN_1(u) - Y_1(u)d\Lambda_1(u)\}\right\}^2 \\
= \;& \frac{1}{p_{11}} EE\left\{\frac{1}{p_{21}^{N1}} + \left(\frac{1}{p_{21}^{R1}} - \frac{1}{p_{21}^{N1}}\right) R \mid T_1, C\right\} \left[\int_0^\tau \frac{\{dN_1(u) - Y_1(u)d\Lambda_1(u)\}}{\bar{F}_1(u)\bar{F}_C(u)}\right]^2 \qquad (1) \\
& \begin{cases} \le \frac{1}{p_{11}p_{21}^{R1}} E\left[\int_0^\tau \frac{\{dN_1(u) - Y_1(u)d\Lambda_1(u)\}}{\bar{F}_1(u)\bar{F}_C(u)}\right]^2 & (p_{21}^{R1} \le p_{21}^{N1}), \\ \le \frac{1}{p_{11}p_{21}^{N1}} E\left[\int_0^\tau \frac{\{dN_1(u) - Y_1(u)d\Lambda_1(u)\}}{\bar{F}_1(u)\bar{F}_C(u)}\right]^2 & (p_{21}^{R1} > p_{21}^{N1}), \end{cases} \\
= \;& \frac{1}{p_{11}\min(p_{21}^{R1}, p_{21}^{N1})} \int_0^\tau \frac{1}{\bar{F}_1(u)\bar{F}_C(u)} d\Lambda_1(u).
\end{aligned}$$

Similarly, for $j = 2$, we have

$$\begin{aligned}
& E\left[\int_0^\tau \frac{W_2}{\bar{F}_2(u)\bar{F}_C(u)}\{dN(u) - Y(u)d\Lambda_2(u)\}\right\}^2 \\
\le \;& \frac{1}{p_{12}\min(p_{22}^{R2}, p_{22}^{N2})} \int_0^\tau \frac{1}{F_2(u)\bar{F}_C(u)} d\Lambda_2(u).
\end{aligned}$$

It follows that the sample size for comparing strategies 111 and 222 is

$$n_K \le \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \sigma_B^2}{\{\bar{F}_2(\tau) - \bar{F}_1(\tau)\}^2},$$

where

$$\sigma_B^2 = \frac{\bar{F}_1^2(\tau)}{p_{11}\min(p_{21}^{R1}, p_{21}^{N1})} \int_0^\tau \frac{d\Lambda_1(u)}{\bar{F}_1(u)\bar{F}_C(u)} + \frac{\bar{F}_2^2(\tau)}{p_{12}\min(p_{22}^{R2}, p_{22}^{N2})} \int_0^\tau \frac{d\Lambda_2(u)}{\bar{F}_2(u)\bar{F}_C(u)}.$$

Similarly, the sample size based on the weighted log rank test with time independent weights and upper bounds on variances is

$$n_L \leq \left\{ \frac{1}{p_{11}\min(p_{21}^{R1}, p_{21}^{N1})} + \frac{1}{p_{12}\min(p_{22}^{R2}, p_{22}^{N2})} \right\} \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{\xi^2 \int_0^\tau \bar{F}_C(u) dF_1(u)},$$

where $\xi$ is the log hazard ratio between $T_1$ and $T_2$.

From (1) we can see that, if the randomization probabilities are discrete uniform in the second-stage randomization and the number of options at the second stage are the same regardless of prior stage treatment, then the upper bounds are exact and there is no conservatism in the sample sizes. This was the case in the trial for drug addicted pregnant women described above. In this case, the weights are actually unnecessary. Of course, this cannot occur in designs in which some subjects are not rerandomized, for instance, in designs in which all responders are not rerandomized, implying that the number of options for these subjects is 1.

For a second example, consider a design in which only nonresponders to the initial treatment $A_1 = 1$ are rerandomized to one of two second-stage treatments, while all other subjects are given a fixed second-stage treatment, as in the autism trial mentioned above. In this design, there are three possible strategies: strategy 11, assign treatment $A_1 = 1$ first, and then assign treatment $A_2 = 1$ to nonresponders; strategy 12, assign treatment $A_1 = 1$ first, and assign treatment $A_2 = 2$ to nonresponders; strategy 2, assign treatment $A_1 = 2$ first, and then assign a fixed treatment afterwards, which may or may not depend on the response status. Suppose the randomization probabilities are $\mathrm{pr}(A_1 = 1) = p$ and $\mathrm{pr}(A_2 = 1|R = 0) = q$, where $R$ is the indicator for response. If we use time independent weights, the weight function associated with strategy 11 is the same as the weight function $W_1$ in the paper except the difference in the meaning of $R$, while the weight function associated with strategy 2 is $W_2 = I(A_1 = 2)/(1-p)$. At first, suppose we use the test based on the weighted Kaplan-Meier estimator with time independent weights to test the equivalence of strategies 11 and 2 to size the study. Similarly as in Section 3 in the paper, we need upper bounds on $E\left[\int_0^\tau W_1/\{\bar{F}_1(u)\bar{F}_C(u)\}\{dN(u) - Y(u)d\Lambda_1(u)\}\right]^2$ and $E\left[\int_0^\tau W_2/\{\bar{F}_2(u)\bar{F}_C(u)\}\{dN(u) - Y(u)d\Lambda_2(u)\}\right]^2$, where $\bar{F}_1(u)$, $\bar{F}_2(u)$, $\Lambda_1(t)$ and $\Lambda_2(t)$ are the survival functions and cumulative hazard functions of the potential failure times under strategies 11 and 2, respectively. The formula for the upper bound when $W_1$ is involved is the same as the upper bound in display (2) in the paper since the formula of $W_1$ is unchanged. However, when $W_2$ is involved, we actually do not need an upper bound since the quantity can be calculated precisely as

$$E\left[\int_0^\tau \frac{W_2}{\bar{F}_2(u)\bar{F}_C(u)}\{dN(u) - Y(u)d\Lambda_2(u)\}\right]^2 = \frac{1}{1-p}\int_0^\tau \frac{d\Lambda_2(u)}{\bar{F}_2(u)\bar{F}_C(u)},$$

because there is no response indicator involved in $W_2$. Consequently, the sample size using a test based on the weighted Kaplan-Meier estimator and upper bounds of variances is

$$n_K \leq \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 \sigma_B^2}{\{\bar{F}_2(\tau) - \bar{F}_1(\tau)\}^2},$$

where

$$\sigma_B^2 \quad = \quad \frac{\bar{F}_1^2(\tau)}{pq} \int_0^\tau \frac{d\Lambda_1(u)}{\bar{F}_1(u)\bar{F}_C(u)} + \frac{\bar{F}_2^2(\tau)}{1-p} \int_0^\tau \frac{d\Lambda_2(u)}{\bar{F}_2(u)\bar{F}_C(u)}.$$

Similarly, the sample size derived from the weighted log rank test and upper bounds of variances is

$$n_L \leq \left(\frac{1}{pq} + \frac{1}{1-p}\right) \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{\xi^2 \int_0^\tau \bar{F}_C(t) dF_1(t)},$$

where $\xi$ is the log hazard ratio between the potential failure times under strategies 11 and 2.

Finally, sample size formulae for sequential multiple assignment randomized trials with more than two stages can be obtained in a similar way as for the designs discussed above. Again, the difference is only in the weight functions and the resulting upper bounds of variances, but the idea for obtaining upper bounds and the form of the upper bounds and sample size formulae are similar.

# 2 Asymptotic Results and Proofs

## 2.1 The weighted Kaplan–Meier estimators

The following theorem provides the asymptotic distribution of the weighted Kaplan–Meier estimator.

**Theorem 1** Assume that $\bar{F}_j(t) > \delta_0$, $j = 1, 2$, and $\bar{F}_C(t) > \delta_0$ for some $\delta_0 > 0$. Then

$$n^{1/2}\{\hat{\bar{F}}_{Kj}(t) - \bar{F}_j(t)\} \to_d N\{0, \sigma_{Kj}^2(t)\},$$

in distribution, as $n \to \infty$, $j = 1, 2$, where

$$\sigma_{Kj}^2(t) \quad = \quad \bar{F}_j^2(t) E\left[\int_0^t \frac{W_j}{\bar{F}_j(u)\bar{F}_C(u)} \{dN(u) - Y(u) d\Lambda_j(u)\}\right]^2, \qquad (2)$$

when time independent weights are used and

$$\sigma^2_{Kj}(t) \;=\; \bar{F}^2_j(t)E\left[\int_0^t \frac{W_j(u)}{\bar{F}_j(u)\bar{F}_C(u)}\{dN(u) - Y(u)d\Lambda_j(u)\}\right]^2, \qquad (3)$$

when time dependent weights are used.

*Proof.* We only need to show the proof for $\hat{\bar{F}}_{K1}(t)$ with time dependent weights. The proof for $\hat{\bar{F}}_{K2}(t)$ and proofs when time independent weights are used are parallel.

At first, we note that martingale theory cannot be applied easily in this problem. If the filtration $\mathcal{F}_t$ is defined in the usual way, the process $N(t) - Y(t)d\Lambda(t)$ is a martingale with respect to $\mathcal{F}_t$, where $\Lambda(t)$ is the cumulative hazard function of the failure time $T$. However, our statistics involve weights, which depend on another quantity $S$ which is time until nonresponse to the initial treatment, and it is likely to be dependent with $T$. Since the variable $S$ is not involved in the definition of the filtration $\mathcal{F}_t$, the weights are not predictable with respect to this filtration. Moreover, if one adds $S$ into the definition of $\mathcal{F}_t$ to make the weights predictable, then the compensator of $N(t)$ will no longer be $Y(t)d\Lambda(t)$ and it is hard to find its exact form. Due to this difficulty, we employ the empirical process theory for the proof of this theorem.

Let $X$ be the vector of observed data for a single subject. Let $P$ be the probability measure of $X$. Denote $\mathbb{P}_n f(X) = \sum_{i=1}^n f(X_i)/n$, $Pf = \int f dP$, and $\mathbb{G}_n f = n^{1/2}(\mathbb{P}_n - P)f$ for any function $f$ of $X$. Let $dN_{Wj}(u) = W_j(u)dN(u)$ and $Y_{Wj}(u) = W_j(u)Y(u)$, $j = 1, 2$. At first, by Proposition 2 in Guo and Tsiatis (2005), for any function $\theta(u)$ on the real line,

$$P\int_0^t \frac{\theta(u)}{\bar{F}_1(u)}\{dN_{W1}(u) - Y_{W1}(u)d\Lambda_1(u)\} = 0.$$

It follows from this equality, along with a similar argument as in the proof of Theorem 3.2.3 in Fleming and Harrington (1991), that

$$\begin{aligned} & n^{1/2}\{\hat{\bar{F}}_{K1}(t) - \bar{F}_1(t)\} \\ = \;& -\bar{F}_1(t)\mathbb{G}_n \int_0^t \frac{\hat{\bar{F}}_{K1}(u-)}{\bar{F}_1(u)}\frac{1}{\bar{Y}_{W1}(u)}\{dN_{W1}(u) - Y_{W1}(u)d\Lambda_1(u)\}. \end{aligned} \qquad (4)$$

We first show that the estimator $\hat{\bar{F}}_{K1}(u)$ is uniformly consistent in $[0, t]$, for any $0 < t \leq \tau$. In order to do this, we need to show that some classes of functions are Donsker (van der Vaart and Wellner, 1996, page 81). Define the classes of functions

$$\begin{aligned} \Phi &= \{\phi(u) : \phi(u) \text{ is a monotone function from } [0, t] \text{ to } [\delta_0, 1]\}, \\ \Theta &= \left\{\theta(u) = \frac{\phi_1(u)}{\phi_2(u)} : \phi_1(u) \in \Phi, \phi_2(u) \in \Phi\right\}, \end{aligned}$$

and

$$\mathcal{F} = \left\{ f_\theta(X) = \int_0^t \frac{\theta(u)}{\bar{F}_1(u)} \{dN_{W1}(u) - Y_{W1}(u) d\Lambda_1(u)\} : \theta(u) \in \Theta \right\}.$$

In the following, denote $C$ to be a generic constant. For any real function $f$ defined on $[0, t]$, denote $||f||_1^2 = \int_0^t f^2(u) dF_1(u)$. By Theorem 2.7.5 in van der Vaart and Wellner (1996), the $\varepsilon$-bracketing number of $\Phi$ under the norm $|| \cdot ||_1$ is of order $K = \exp(C/\varepsilon)$ for a positive constant $C$. Let $\phi_1^L(u), \phi_1^U(u), \cdots, \phi_K^L(u), \phi_K^U(u)$ be the set of $\varepsilon$-brackets covering $\Phi$. For any function $\theta(u)$ in $\Theta$, there exist functions $\phi_1(u)$ and $\phi_2(u)$ in $\Phi$ such that $\theta(u) = \phi_1(u)/\phi_2(u)$. Let $\phi_{r_1}^L(u), \phi_{r_1}^U(u)$ and $\phi_{r_2}^L(u), \phi_{r_2}^U(u)$ be $\varepsilon$-brackets for $\phi_1(u)$ and $\phi_2(u)$, respectively. Then $\phi_{r_1}^L(u)/\phi_{r_2}^U(u) \le \theta(u) \le \phi_{r_2}^U(u)/\phi_{r_1}^L(u)$ and

$$\left|\left| \frac{\phi_{r_1}^L(u)}{\phi_{r_2}^U(u)} - \frac{\phi_{r_2}^U(u)}{\phi_{r_1}^L(u)} \right|\right|_1^2 \le C\{||\phi_{r_1}^L(u) - \phi_{r_1}^U(u)||_1^2 + ||\phi_{r_2}^L(u) - \phi_{r_2}^U(u)||_1^2\}.$$

This implies that the $\varepsilon$-bracketing number of $\Theta$ is of the same order as that of $\Phi$, which we also denote by $K = \exp(C/\varepsilon)$. Therefore, there exist functions $\theta_j^L(u) \in \Theta, \theta_j^U(u) \in \Theta, 1 \le j \le K$ such that $||\theta_j^L - \theta_j^U||_1 \le \varepsilon, 1 \le j \le K$, and for any $\theta(u) \in \Theta$, $\theta_i^L(u) \le \theta(u) \le \theta_i^U(u)$ for some $1 \le i \le K$. Consequently, the function $f_\theta(X)$ in $\mathcal{F}$ satisfies

$$f_\theta(X) \ge \int_0^t \frac{\theta_i^L(u)}{\bar{F}_1(u)} dN_{W1}(u) - \int_0^t \frac{\theta_i^U(u)}{\bar{F}_1(u)} Y_{W1}(u) d\Lambda_1(u) \equiv f_i^L(X)$$

and

$$f_\theta(X) \le \int_0^t \frac{\theta_i^U(u)}{\bar{F}_1(u)} dN_{W1}(u) - \int_0^t \frac{\theta_i^L(u)}{\bar{F}_1(u)} Y_{W1}(u) d\Lambda_1(u) \equiv f_i^U(X),$$

and moreover, if we define $||f||_2^2 = Pf^2$, then

$$\begin{aligned}
||f_i^L - f_i^U||_2 &= \left|\left| \int_0^t \frac{\theta_i^L(u) - \theta_i^U(u)}{\bar{F}_1(u)} dN_{W1}(u) - \int_0^t \frac{\theta_i^U(u) - \theta_i^L(u)}{\bar{F}_1(u)} Y_{W1}(u) d\Lambda_1(u) \right|\right|_2 \\
&\le \left|\left| \int_0^t \frac{\theta_i^L(u) - \theta_i^U(u)}{\bar{F}_1(u)} dN_{W1}(u) \right|\right|_2 + \left|\left| \int_0^t \frac{\theta_i^U(u) - \theta_i^L(u)}{\bar{F}_1(u)} Y_{W1}(u) d\Lambda_1(u) \right|\right|_2 \\
&\le C \left\{ \left[ \int_0^\tau \{\theta_i^L(u) - \theta_i^U(u)\}^2 dF_1(u) \right]^{\frac{1}{2}} + \left[ \int_0^\tau \{\theta_i^U(u) - \theta_i^L(u)\}^2 d\Lambda_1(u) \right]^{\frac{1}{2}} \right\} \\
&\le C \left\{ \left[ \int_0^t \{\theta_i^L(u) - \theta_i^U(u)\}^2 dF_1(u) \right]^{\frac{1}{2}} + \left[ \int_0^t \{\theta_i^U(u) - \theta_i^L(u)\}^2 dF_1(u) \right]^{\frac{1}{2}} \right\} \\
&\le C\varepsilon.
\end{aligned}$$

It follows that the functions $f_1^l, f_1^U, \cdots, f_K^l, f_K^U$ are $C\varepsilon$ brackets under the $L_2(P)$ norm and they cover $\mathcal{F}$. Hence the $\varepsilon$-bracketing number of $\mathcal{F}$ under the $L_2(P)$ norm is also of order

$\exp(C/\varepsilon)$, and therefore by Theorem 2.5.6 in van der Vaart and Wellner (1996), $\mathcal{F}$ is a $P$-Donsker class. It follows that, by the continuous mapping theorem,

$$\begin{aligned} & \left|\mathbb{G}_n \int_0^t \frac{\hat{\bar{F}}_{K1}(u-)}{\bar{F}_1(u)} \frac{1}{\bar{Y}_{W1}(u)} \{dN_{W1}(u) - Y_{W1}(u) d\Lambda_1(u)\}\right| \\ \leq & \sup_{\theta\in\Theta} \left|\mathbb{G}_n \int_0^t \frac{\theta(u)}{\bar{F}_1(u)} \{dN_{W1}(u) - Y_{W1}(u) d\Lambda_1(u)\}\right| \\ \to & \sup_{\theta\in\Theta} |\mathbb{G} f_\theta|, \end{aligned}$$

in distribution, as $n \to \infty$, where $\{\mathbb{G}f : f \in \mathcal{F}\}$ is a $P$-Brownian bridge process. In light of (4), this implies that $\hat{\bar{F}}_{K1}(t) \to \bar{F}_1(t)$ in probability, with rate $1/n^{1/2}$. Since both $\hat{\bar{F}}_{K1}(\cdot)$ and $\bar{F}_1(\cdot)$ are increasing and bounded functions, and $\bar{F}_1(\cdot)$ is continuous, it follows that

$$\sup_{u\in[0,t]} |\hat{\bar{F}}_{K1}(u) - \bar{F}_1(u)| \to 0, \text{ and } \sup_{u\in[0,t]} |\hat{\bar{F}}_{K1}(u-) - \bar{F}_1(u)| \to 0, \tag{5}$$

in probability. This holds for every $t \in [0, \tau]$.

To show the asymptotic normality of $\hat{\bar{F}}_{K1}(t)$, we write

$$\begin{aligned} \hat{\bar{F}}_{K1}(t) - \bar{F}_1(t) &= -\bar{F}_1(t) \left[ (\mathbb{P}_n - P) \int_0^t \frac{1}{y_{W1}(u)} \{dN_{W1}(u) - Y_{W1}(u) d\Lambda_1(u)\} \right. \\ & \quad \left. + (\mathbb{P}_n - P) D_n(X) \right], \end{aligned} \tag{6}$$

where $y_{W1}(u) = E\{W_1 Y(u)\} = \bar{F}_1(u)\bar{F}_C(u)$ and

$$D_n(X) = \int_0^t \left\{ \frac{1}{y_{W1}(u)} - \frac{\hat{\bar{F}}_{K1}(u-)}{\bar{F}_1(u)} \frac{1}{\bar{Y}_{W1}(u)} \right\} \{dN_{W1}(u) - Y_{W1}(u) d\Lambda_1(u)\}.$$

Let $\theta_n(u) = \hat{\bar{F}}_{K1}(u-)/\bar{Y}_{W1}(u)$ and $\theta_0(u) = 1/\bar{F}_C(u)$. Then by (5) and the law of large numbers, $||\theta_n - \theta_0||_\infty \equiv \sup_{0\leq u\leq\tau} |\theta_n(u) - \theta_0(u)| \to 0$, as $n \to \infty$. Since the class of functions $\mathcal{F}$ is $P$-Donsker, by equicontinuity (see van der Vaart and Wellner, 1996, page 89), for large $n$ and some sequence $\delta_n \to 0$, with high probability, we have

$$\begin{aligned} |n^{1/2}(\mathbb{P}_n - P) D_n(X)| &= |\mathbb{G}_n\{f_{\theta_n}(X) - f_{\theta_0}(X)\}| \\ &\leq \sup_{||\theta-\theta_0||_\infty \leq \delta_n} |\mathbb{G}_n\{f_\theta(X) - f_{\theta_0}(X)\}| \\ &\leq \sup_{||f_\theta - f_{\theta_0}||_2 \leq C\delta_n} |\mathbb{G}_n\{f_\theta(X) - f_{\theta_0}(X)\}| \\ &\to 0. \end{aligned}$$

Therefore, (6) can be rewritten as

$$n^{1/2}\{\hat{\bar{F}}_{K1}(t) - \bar{F}_1(t)\} = -\bar{F}_1(t)\mathbb{G}_n \int_0^t \frac{1}{y_{W1}(u)} \{dN_{W1}(u) - Y_{W1}(u) d\Lambda_1(u)\} + o_p(1), \tag{7}$$

from which the asymptotic normality of $\hat{\bar{F}}_{K1}(t)$ follows, with an asymptotic variance that is stated in the theorem. □

Although it is not of interest in this paper, for completeness, we now demonstrate how we can construct a test statistic for testing for strategies 11 and 12, which is similar to testing for strategies 21 and 22. Denote the survival function of $T_{12}$, the potential failure time under strategy 12, by $\bar{F}_3(t)$, and denote its weighted Kaplan–Meier estimator by $\hat{\bar{F}}_{K3}(t)$. Unlike strategies with different initial treatments, strategies 11 and 12 share subjects, so $\hat{\bar{F}}_{K1}(t)$ and $\hat{\bar{F}}_{K3}(t)$ are correlated, but we can obtain their joint asymptotic distribution. Without loss of generality, assume time dependent weights are used. By the proof of Theorem 1, we can obtain the following equality similarly as (7):

$$n^{1/2}\{\hat{\bar{F}}_{K3}(t) - \bar{F}_3(t)\} = -\bar{F}_3(t)\mathbb{G}_n \int_0^t \frac{1}{y_{W3}(u)}\{dN_{W3}(u) - Y_{W3}(u)d\Lambda_3(u)\} + o_p(1), \qquad (8)$$

where $\Lambda_3(t)$ is the cumulative hazard function of $T_{12}$, $y_{W3}(u) = \bar{F}_3(u)\bar{F}_C(u)$, $dN_{W3}(u) = W_3(u)dN(u)$, $Y_{W3}(u) = W_3(u)Y(u)$, and

$$W_3(u) = \frac{I(A_1 = 1)}{p}\left\{1 - R(u) + \frac{I(A_2 = 2)}{1-q}R(u)\right\}$$

is the time dependent weight function for strategy 12. By (7) and (8), $n^{1/2}\{\hat{\bar{F}}_{K1}(t) - \bar{F}_1(t), \hat{\bar{F}}_{K3}(t) - \bar{F}_3(t)\}$ converges in distribution to $N(0, \Sigma)$, as $n \to \infty$, where

$$\Sigma = \left\{ \begin{array}{cc} \sigma^2_{K1}(t) & \sigma_{K13}(t) \\ \sigma_{K13}(t) & \sigma^2_{K3}(t) \end{array} \right\}$$

with $\sigma^2_{K3}(t)$ defined by (3) for $j = 3$, and

$$\sigma_{K13}(t) = \bar{F}_1(t)\bar{F}_3(t)E \prod_{j\in\{1,3\}} \int_0^t \frac{W_j(u)}{\bar{F}_j(u)\bar{F}_C(u)}\{dN(u) - Y(u)d\Lambda_j(u)\}. \qquad (9)$$

From this result, a test statistic for testing $H_0 : \bar{F}_1(t) = \bar{F}_3(t)$ for some fixed $t$ using weighted Kaplan–Meier estimators can be constructed similarly as testing $H_0 : \bar{F}_1(t) = \bar{F}_2(t)$ in the paper. The only difference is that here we need to estimate the covariance $\sigma_{K13}(t)$ by an empirical estimator based on (9).

## 2.2 The weighted sample proportion estimator

This estimator is a modification of the third weighted sample proportion estimator of $\bar{F}_j(t)$, for $j = 1, 2$, in Lunceford et al. (2002) by using time dependent weights as follows. Denote

$G_j(t,u) = E\{I(u \le T_{j1} \le t)\}/\mathrm{pr}(T > u)$, and $G_{W_j}(u) = E[\{W_j(T) - 1\}I(T \ge u)]/\mathrm{pr}(T \ge u)$, $j = 1, 2$. Denote

$$L_j^\alpha(t,u) = \{W_j(T)I(U \le t) - G_j(t,u)\} \times \{W_j(T) - 1 - G_{W_j}(u)\}I(T \ge u)$$

and $G_j^\alpha(u) = \{W_j(T) - 1 - G_{W_j}(u)\}^2 I(T \ge u)$. Define

$$\begin{aligned}
\hat{G}_{W_j}(u) &= \frac{1}{n\hat{\bar{F}}(u)} \sum_{i=1}^n \Delta_i \{W_{ji}(U_i) - 1\} \frac{I(U_i \ge u)}{\hat{\bar{F}}_C(U_i)}, \\
\hat{G}_j(t,u) &= \frac{1}{n\hat{\bar{F}}(u)} \sum_{i=1}^n \Delta_i W_{ji}(U_i) I(U_i \le t) \frac{I(U_i \ge u)}{\hat{\bar{F}}_C(U_i)},
\end{aligned}$$

$$\hat{E}\{L_j^\alpha(t,u)\} = \frac{1}{n} \sum_{i=1}^n \Delta_i \{W_{ji}(U_i)I(U_i \le t) - \hat{G}_j(t,u)\} \times \{W_{ji}(U_i) - 1 - \hat{G}_{W_j}(u)\} \frac{I(U_i \ge u)}{\hat{\bar{F}}_C(U_i)},$$

and

$$\hat{E}\{G_j^\alpha(u)\} = \frac{1}{n} \sum_{i=1}^n \Delta_i \{W_{ji}(U_i) - 1 - \hat{G}_{W_j}(u)\}^2 \frac{I(U_i \ge u)}{\hat{\bar{F}}_C(U_i)}.$$

Recall that $\hat{\bar{F}}(u)$ is the usual Kaplan–Meier estimator of $\bar{F}(u)$, the survival function of $T$. Also define

$$\begin{aligned}
A_{1j} &= \frac{1}{n} \sum_{i=1}^n \Delta_i W_{ji}(U_i) \{W_{ji}(U_i) - 1\} \frac{I(U_i \le t)}{\hat{\bar{F}}_C(U_i)} + \int_0^\tau dN^c(u) \{\hat{\bar{F}}_C(u) Y(u)\}^{-1} \hat{E}\{L_j^\alpha(t,u)\} \\
A_{2j} &= \frac{1}{n} \sum_{i=1}^n \{W_{ji}(U_i) - 1\}^2 + \int_0^\tau dN^c(u) \{\hat{\bar{F}}_C(u) Y(u)\}^{-1} \hat{E}\{G_j^\alpha(u)\},
\end{aligned}$$

and $\hat{\alpha}_j = A_{1j}/A_{2j}$, $j = 1, 2$, where $N^c(u) = I(U \le u, C \le T)$ and $\hat{\bar{F}}_C(u)$ is the usual Kaplan–Meier estimator of $\bar{F}_C(u)$. The modified sample proportion estimator of $\bar{F}_j(t)$ is define as $\hat{\bar{F}}_{Sj}(t) = 1 - \hat{F}_{Sj}(t)$, where

$$\hat{F}_{Sj}(t) = \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i W_{ji}(U_i)}{\hat{\bar{F}}_C(U_i)} I(U_i \le t) - \hat{\alpha}_j \frac{1}{n} \sum_{i=1}^n \frac{\Delta_i}{\hat{\bar{F}}_C(U_i)} \{W_{ji}(U_i) - 1\}, \; j = 1, 2, \tag{10}$$

Clearly, the $\hat{\alpha}_j$ defined above is a consistent estimator of $\alpha_j$, which is given by

$$\begin{aligned}
\alpha_j = \Bigg( & E[W_{ji}(U_i)\{W_{ji}(U_i) - 1\}I(U_i \le t)] + \int_0^\tau \lambda^c(u) \bar{F}_C(u)^{-1} E\{L_j^\alpha(t,u)\} du \Bigg) \\
& \div \left[ E\{W_{ji}(U_i) - 1\}^2 + \int_0^\tau \lambda^c(u) \bar{F}_C(u)^{-1} E\{G_j^\alpha(u)\} du \right], \; j = 1, 2,
\end{aligned}$$

where $\lambda^c(u)$ is the hazard function of the censoring time $C$. Note that, arguing in a similar way as in Lunceford et al. (2002), this choice of $\alpha_j$ minimizes the variance of the influence function corresponding to the estimator of $F_j(t)$ by solving the equation

$$\sum_{i=1}^{n} \frac{\Delta_i}{\hat{\bar{F}}_C(U_i)}[W_{ji}(U_i)I(U_i \le t) - F_j(t) - \alpha_j\{W_{ji}(U_i) - 1\}] = 0.$$

The following theorem shows the asymptotic properties of this estimator. The proof for this theorem is omitted here, because it is parallel to the proof for the unmodified weighted sample proportion estimator in Lunceford et al. (2002).

**Theorem 2** Assume that $\bar{F}_j(t) > \delta_0$, $j = 1, 2$, and $\bar{F}_C(t) > \delta_0$ for some $\delta_0 > 0$. Then

$$n^{1/2}\{\hat{\bar{F}}_{Sj}(t) - \bar{F}_j(t)\} \to N\{0, \sigma^2_{Sj}(t)\}$$

in distribution, $j = 1, 2$, as $n \to \infty$, where

$$\begin{aligned} \sigma^2_{Sj}(t) &= E[W_j(T)I(T \le t) - F_j(t) - \alpha_j\{W_j(T) - 1\}]^2 \\ &\quad + \int_0^t \frac{E\{L_j(t,u)\}^2}{\bar{F}_C(u)}\lambda^c(u)du, \end{aligned}$$

with

$$L_j(t, u) = [W_j(T)I(T \le t) - G_j(t, u) - \alpha_j\{W_j(T) - 1 - G_{W_j}(u)\}]I(T \ge u).$$

## 2.3 The weighted log rank statistics

We derive the asymptotic properties of the weighted log rank test statistic using a proportional hazards assumption and under a local alternative. As described in the paper, we use the local alternative,

$$H_n : \lambda_2^n(t) = \lambda_1(t)\exp(\gamma/n^{1/2}),\ n \ge 1,$$

where $\gamma$ is a constant. To make it clear that the hazard function $\lambda_2(t)$ depends on $n$ under the local alternative hypothesis, we denote it by $\lambda_2^n(t)$. We denote the distribution of the observed data under $H_n$ as $P_n$, and denote the distribution under the null hypothesis, which corresponds to $\gamma = 0$, as $P_0$. The theorem below gives the asymptotic distribution of the weighted log rank test statistic.

**Theorem 3** Assume that $\bar{F}_1(\tau) > \delta_0$ and $\bar{F}_C(\tau) > \delta_0$ for some $\delta_0 > 0$. Then

$$n^{1/2}L_n \to N\{\mu_L, (\sigma^2_{L1} + \sigma^2_{L2})/4\}$$

in distribution, under $P_n$, as $n \to \infty$, where $\mu_L = \gamma \int_0^\tau \bar{F}_C(t) dF_1(t)/2$ and

$$\sigma_{Lj}^2 = P_0 \left[ \int_0^\tau W_j \{ dN(t) - Y(t) d\Lambda_1(t) \} \right]^2, \ j = 1, 2,$$

when time independent weights are used, and

$$\sigma_{Lj}^2 = P_0 \left[ \int_0^\tau W_j(t) \{ dN(t) - Y(t) d\Lambda_1(t) \} \right]^2, \ j = 1, 2,$$

when time dependent weights are used.

*Proof.* In the following we assume that the weights are time dependent. The proof is similar when time independent weights are used.

Define

$$\mathcal{F} = \left\{ \int_0^\tau \theta(u) \{ dN_{W2}(u) - Y_{W2}(u) d\Lambda_1(u) \} : \theta(u) \in \Theta \right\},$$

where $\Theta$ is as defined in the proof of Theorem 1. We first prove that $n^{1/2}(\mathbb{P}_n - P_n)$ converges to $\mathbb{G}_{P_0}$ in $\ell^\infty(\mathcal{F})$ under $P_n$, as $n \to \infty$, where $\{\mathbb{G}_{P_0} f : f \in \mathcal{F}\}$ is a $P_0$-Brownian bridge process. The proof of the asymptotic normality of $L_n$ relies on the asymptotic equi-continuity of the process $n^{1/2}(\mathbb{P}_n - P_n)$ implied by this result. We use Theorem 2.8.9 in van der Vaart and Wellner (1996) for the proof. In order to use that theorem, we need to verify the following three conditions:

1. $\sup_{f,g \in \mathcal{F}} |\rho_{P_n}(f,g) - \rho_{P_0}(f,g)| \to 0$, where $\rho_P(f,g) \equiv \text{var}_P(f-g)$.
2. There exists an envelope function $F$ of $\mathcal{F}$ such that $\limsup_{n\to\infty} P_n F^2 I(F \geq \varepsilon n^{1/2}) = 0$, and $P_n F^2 = O(1)$.
3. Both $\mathcal{F}_{\delta,P_n} = \{f - g : f, g \in \mathcal{F}, ||f-g||_{P_n,2} < \delta\}$ and $\mathcal{F}_\infty = \{(f-g)^2 : f, g \in \mathcal{F}, ||f-g||_{P_n,2} < \delta\}$ are $P_n$-measurable (van der Vaart and Wellner, 1996, page 110) for every $\delta > 0$ and $n$.

We first check condition 1. Let

$$f = \int_0^\tau \theta_1(u) \{ dN_{W2}(u) - Y_{W2}(u) d\Lambda_1(u) \},$$

and

$$g = \int_0^\tau \theta_2(u) \{ dN_{W2}(u) - Y_{W2}(u) d\Lambda_1(u) \},$$

for some functions $\theta_1(u), \theta_2(u) \in \Theta$. Let $f_P(t_{21}, s)$ and $f_P(t_{21})$ be the probability density functions of $(T_{21}, S)$ and $T_{21}$ under probability measure $P$ of the observed data, and let $F_C(c)$ be the distribution function of the censoring time $C$. Denoting $Y_{21}(u) = I(T_{21} \geq u, C \geq u)$, by our assumptions on $\Theta$, we can write

$$\begin{aligned}
\rho_P(f,g) &= P\Bigg[\{\theta_1(T_{21}) - \theta_2(T_{21})\} I(T_{21} \leq C) I(T_{21} \leq \tau) W_2(T_{21}) \\
&\qquad - \int_0^\tau \{\theta_1(u) - \theta_2(u)\} W_2(u) Y_{21}(u) d\Lambda_1(u)\Bigg]^2 \\
&= \frac{1}{1-p} P\left\{I(S > T_{21}) + \frac{I(S \leq T_{21})}{1-q}\right\} \Big[\{\theta_1(T_{21}) - \theta_2(T_{21})\} I(T_{21} \leq C) I(T_{21} \leq \tau) \\
&\qquad - \int_0^\tau \{\theta_1(u) - \theta_2(u)\} Y_{21}(v) d\Lambda_1(u)\Big]^2 \\
&= \int_0^\infty \int_0^\infty \int_0^\infty K(t_{21}, s, c) f_P(t_{21}, s) dt_{21} ds dF_C(c), \qquad (11)
\end{aligned}$$

for a function $K(t_{21}, s, c)$ that can be bounded by a constant $A$ and is independent of $n$. Under $H_n$, we have $\Lambda_2^n(u) = \Lambda_1(u)\exp(\gamma/n^{1/2})$, where $\Lambda_2^n(u)$ is the cumulative hazard function of $T_{21}$ under $H_n$. This implies that

$$f_{P_n}(t_{21}) - f_{P_0}(t_{21}) = f_{P_0}(t_{21}) \left[\exp\left(\frac{\gamma}{n^{1/2}}\right) \{\bar{F}_1(t_{21})\}^{\exp\left(\frac{\gamma}{n^{1/2}}\right)-1} - 1\right].$$

This, combined with the fact that $f_{P_n}(s \mid t_{21}) = f_{P_0}(s \mid t_{21})$, yields

$$f_{P_n}(t_{21}, s) - f_{P_0}(t_{21}, s) = f_{P_0}(t_{21}, s) \left[\exp\left(\frac{\gamma}{n^{1/2}}\right) \{\bar{F}_1(t_{21})\}^{\exp\left(\frac{\gamma}{n^{1/2}}\right)-1} - 1\right]. \qquad (12)$$

Now by (11) and (12), it follows that, for any $f, g \in \mathcal{F}$,

$$\begin{aligned}
&|\rho_{P_n}(f,g) - \rho_{P_0}(f,g)| \\
&\leq \int_0^\infty \int_0^\infty \int_0^\infty K(t_{21}, s, c) |f_{P_n}(t_{21}, s) - f_{P_0}(t_{21}, s)| dt_{21} ds dF_C(c) \\
&\leq A \int_0^\infty \int_0^\infty \int_0^\infty f_{P_0}(t_{21}, s) \left|\exp\left(\frac{\gamma}{n^{1/2}}\right) \{\bar{F}_1(t_{21})\}^{\exp\left(\frac{\gamma}{n^{1/2}}\right)-1} - 1\right| dt_{21} ds dF_C(c). \quad (13)
\end{aligned}$$

Now we claim, by the dominated convergence theorem, that the right hand side of (13) converges to 0 as $n \to \infty$. At first, the absolute value in the integrand converges to 0 as $n \to \infty$. In addition, when $\gamma > 0$, the absolute value in the integrand is bounded by $\exp(\gamma) + 1$, and when $\gamma < 0$, it is bounded by $\{\bar{F}_1(t_{21})\}^{\exp(\gamma)-1} + 1$. In the latter case, plugging the absolute value by this bound, the integral is bounded by $P_0\{\bar{F}_1(T_{11})\}^\alpha + 1$, where $\alpha = \exp(\gamma) - 1 < 0$. Since $\bar{F}_1(T_{11})$ is uniformly distributed in $[0,1]$ and $\alpha > -1$, it follows that$P_0\{\bar{F}_1(T_{11})\}^\alpha < \infty$, and hence the dominated convergence theorem applies.

To check condition 2, note that the functions $\int_0^\tau \theta(u)\{dN_{W2}(u) - Y_{W2}(u)d\Lambda_1(u)\}$ are bounded by a constant under our assumptions. So we can choose the envelope function $F$ to be the upper bound. For such an envelope function, the first part of condition (2) is obviously satisfied. And we also have that $P_n F^2 = O(1)$.

Finally, the $P_n$-measurability of $\mathcal{F}_{\delta,P_n}$ and $\mathcal{F}_\infty^2$ in condition 3 follows since $\theta$ is a monotone function divided by another monotone function. For any monotone function, it is the (pointwise) limit of a series of step functions of the form $\sum_{i=1}^n c_i I(t_{i-1} < t \le t_i)$, where all the $t_i$s are rational numbers. Since the set of all such functions is countable, by Example 2.3.4 in van der Vaart and Wellner (1996), both $\mathcal{F}_{\delta,P_n}$ and $\mathcal{F}_\infty^2$ are $P_n$-measurable.

Now we conclude from Theorem 2.8.9 in van der Vaart and Wellner (1996) that $n^{1/2}(\mathbb{P}_n - P_n)$ converges to $\mathbb{G}_{P_0}$ in $\ell^\infty(\mathcal{F})$ under $P_n$, as $n \to \infty$.

Similarly, if we define

$$\mathcal{F}' = \left\{ \int_0^t \theta(u)\{dN_{W1}(u) - Y_{W1}(u)d\Lambda_1(u)\} : \theta(u) \in \Theta \right\},$$

then we can also show that $n^{1/2}(\mathbb{P}_n - P_n)$ converges to $\mathbb{G}_{P_0}$ in $\ell^\infty(\mathcal{F}')$ under $P_n$.

Before we can show the asymptotic normality of $G_n$, we need to show that

$$\sup_{t\in[0,\tau]} \left| \frac{\bar{Y}_{Wj}(t)}{\bar{Y}_{W1}(t) + \bar{Y}_{W2}(t)} - \frac{1}{2} \right| \to 0, j = 1, 2,$$

in probability, as $n \to \infty$. This follows from the fact that $\sup_{t\in[0,\tau]} |\bar{Y}_{Wj}(t) - y_{W1}(t)| \to 0$ in probability, $j = 1, 2$, which is a consequence of the asymptotic normality of $n^{1/2}\{\bar{Y}_{Wj}(t) - y_{Wj}(t)\}$ under $P_n$. The latter can be proved by the Lindeberg-Feller central limit theorem, the details of which are omitted here. From these results, it follows that, under $P_n$,

$$\begin{aligned} n^{1/2} L_n &= n^{1/2}(\mathbb{P}_n - P_n) \int_0^\tau \frac{\bar{Y}_{W2}(t)}{\bar{Y}_{W1}(t) + \bar{Y}_{W2}(t)} \{dN_{W1}(t) - Y_{W1}(t)d\Lambda_1(t)\} \\ &\quad -n^{1/2}(\mathbb{P}_n - P_n) \int_0^\tau \frac{\bar{Y}_{W1}(t)}{\bar{Y}_{W1}(t) + \bar{Y}_{W2}(t)} \{dN_{W2}(t) - Y_{W2}(t)d\Lambda_2^n(t)\} \\ &\quad +n^{1/2} \int_0^\tau \frac{\bar{Y}_{W1}(t)\bar{Y}_{W2}(t)}{\bar{Y}_{W1}(t) + \bar{Y}_{W2}(t)} \{\lambda_1(t) - \lambda_2^n(t)\}dt \\ &= \frac{n^{1/2}}{2}(\mathbb{P}_n - P_n) \int_0^\tau \{dN_{W1}(t) - Y_{W1}(t)d\Lambda_1(t)\} \\ &\quad -\frac{n^{1/2}}{2}(\mathbb{P}_n - P_n) \int_0^\tau \{dN_{W2}(t) - Y_{W2}(t)d\Lambda_1(t)\} \\ &\quad +\frac{\gamma}{2} \int_0^\tau \bar{F}_1(t)\bar{F}_C(t)d\Lambda_1(t) + o_{P_n}(1). \end{aligned} \tag{14}$$

Again by the Lindeberg-Feller central limit theorem, the first term on the right hand side of the above equality converges in distribution to $N(0, \sigma^2_{L1}/4)$, and the second term converges to $N(0, \sigma^2_{L2}/4)$, both under $P_n$, where

$$\sigma^2_{Lj} = P_0 \left[ \int_0^\tau W_j \{dN(t) - Y(t) d\Lambda_1(t)\} \right]^2, \; j = 1, 2.$$

Finally, $G_n/n^{1/2} \rightarrow_d N\{\mu_L, (\sigma^2_{L1} + \sigma^2_{L2})/4\}$ under $P_n$, where $\mu_L = \gamma \int_0^\tau \bar{F}_C(t) d\Lambda_1(t)/2 = \gamma \int_0^\tau \bar{F}_C(t)\, dF_1(t)/2$. $\square$

We used the independence of the first and second terms on the right hand side of (14) to obtain the asymptotic variance formula for $G_n$. In a weighted log rank test where the two strategies that are compared in the test start with the same initial treatment, the above independence does not hold. In such cases, one needs to add a covariance term, i.e., the covariance between the first two integrals on the right hand side of (14). Since this covariance is the expectation of the product of the two terms, it can also be estimated empirically from the observed data.

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