Web-based Supplemental Materials for
“A Proportional Hazards Cure Model for the
Analysis of Time to Event with Frequently
Unidentifiable Causes”

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Web Appendix A: Derivation of Conditional Expectations

In the equations that follow, please note that for notational simplicity, we omit the
superscript \((m)\) for the parameters on the right hand side of the equations.

\[
E(\tau_i \mid \Theta^{(m)}, O_i) \tag{A1}
\]

\[
= P(\tau_i = 1 \mid \min(T_2, T_1) = x_i, Z_i)
\]

\[
= \lim_{\Delta \to 0} \frac{P(\tau_i = 1, \min(T_2, T_1) \in \{x_i, x_i + \Delta\} \mid Z_i) / \Delta}{P(\min(T_2, T_1) \in \{x_i, x_i + \Delta\} \mid Z_i) / \Delta}
\]

\[
= \left\{ 1 - F_{T_1}(x_i) \right\} \alpha f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} \alpha f_{T_1}(x_i)
\]

\[
f_{T_2}(x_i) \left\{ 1 - \alpha F_{T_1}(x_i) \right\} + \alpha f_{T_1}(x_i) \left\{ 1 - F_{T_2}(x_i) \right\}
\]

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\[ E(\tau_i^* \mid \Theta^{(m)}, O_i) \]
\[ = P(\tau_i^* = 1 \mid \min(T_2, T_1) > C, Z_i) \] 
\[ = \frac{P(\tau_i^* = 1, \min(T_2, T_1) > C \mid Z_i)}{P(\min(T_2, T_1) > C \mid Z_i)} \] 
\[ = \frac{P(\tau_i^* = 1, T_2 > C, T_1 > C \mid Z_i)}{P(T_2 > C, T_1 > C \mid Z_i)} \] 
\[ = \frac{\alpha \{1 - F_{T_1}(C)\}}{(1 - \alpha) + \alpha \{1 - F_{T_1}(C)\}} \]

\[ E(\zeta_i \mid \Theta^{(m)}, O_i, \tau_i = 1) \] 
\[ = P(\zeta_i = 1 \mid \tau_i = 1, \min(T_2, T_1) = x_i, Z_i) \] 
\[ = \lim_{\Delta \to 0} \frac{P(\zeta_i = 1, \min(T_2, T_1) \in \{x_i, x_i + \Delta\} \mid \tau_i = 1, Z_i) / \Delta}{P(\min(T_2, T_1) \in \{x_i, x_i + \Delta\} \mid \tau_i = 1, Z_i) / \Delta} \] 
\[ = \lim_{\Delta \to 0} \frac{P(T_2 \in \{x_i, x_i + \Delta\}, T_1 > T_2 \mid \tau_i = 1, Z_i) / \Delta}{P(\min(T_2, T_1) \in \{x_i, x_i + \Delta\} \mid \tau_i = 1, Z_i) / \Delta} \] 
\[ = \frac{\{1 - F_{T_1}(x_i)\} f_{T_2}(x_i)}{\{1 - F_{T_1}(x_i)\} f_{T_2}(x_i) + P(T_2 > x_i \mid T_1 = x_i, \tau_i = 1, Z_i) f_{T_1}(x_i)} \] 
\[ \frac{\{1 - F_{T_1}(x_i)\} f_{T_2}(x_i) + (1 - F_{T_2}(x_i)) f_{T_1}(x_i)}{\{1 - F_{T_1}(x_i)\} f_{T_2}(x_i) + (1 - F_{T_2}(x_i)) f_{T_1}(x_i)} \]
\[ E(\zeta_i \tau_i \mid \Theta^{(m)}, O_i) \]
\[ = E(\tau_i E(\zeta_i \mid \tau_i, \Theta^{(m)}, O_i) \mid \Theta^{(m)}, O_i) \]
\[ = 1 \cdot P(\tau_i = 1 \mid \Theta^{(m)}, O_i) E(\zeta_i \mid \tau_i = 1, \Theta^{(m)}, O_i) \]
\[ + 0 \cdot P(\tau_i = 0 \mid \Theta^{(m)}, O_i) E(\zeta_i \mid \tau_i = 0, \Theta^{(m)}, O_i) \]
\[ = E(\tau_i \mid \Theta^{(m)}, O_i) E(\zeta_i \mid \tau_i = 1, \Theta^{(m)}, O_i) \]
\[ = \left\{ 1 - F_{T_1}(x_i) \right\} \alpha f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} \alpha f_{T_1}(x_i) \]
\[ \frac{\{1 - F_{T_2}(x_i)\} \{1 - \alpha F_{T_1}(x_i)\} + \alpha f_{T_1}(x_i) \{1 - F_{T_2}(x_i)\}}{\{1 - F_{T_1}(x_i)\} f_{T_2}(x_i)} \]
\[ \times \left( \frac{1 - F_{T_1}(x_i)}{f_{T_2}(x_i)} + \frac{1 - F_{T_2}(x_i)}{f_{T_1}(x_i)} \right) \]

\[ E(\zeta_i \mid \Theta^{(m)}, O_i) \]
\[ = P(\zeta_i = 1, \tau_i = 1 \mid \Theta^{(m)}, O_i) + P(\zeta_i = 1, \tau_i = 0 \mid \Theta^{(m)}, O_i) \]
\[ = E(\zeta_i \tau_i \mid \Theta^{(m)}, O_i) + P(\zeta_i = 1, \tau_i = 0, \Theta^{(m)}, O_i) P(\tau_i = 0 \mid \Theta^{(m)}, O_i) \]
\[ = E(\zeta_i \tau_i \mid \Theta^{(m)}, O_i) + P(\zeta_i = 1 \mid \tau_i = 0, \min(T_2, T_1) = x_i) P(\tau_i = 0 \mid \Theta^{(m)}, O_i) \]
\[ = \frac{\left\{ 1 - F_{T_1}(x_i) \right\} \alpha f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} \alpha f_{T_1}(x_i)}{\left\{ 1 - F_{T_1}(x_i) \right\} \alpha f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} \alpha f_{T_1}(x_i) + (1 - \alpha) f_{T_2}(x_i) \}
\[ \times \left\{ 1 - F_{T_1}(x_i) \right\} f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} f_{T_1}(x_i) \]
\[ + 1 \cdot \left\{ 1 - E(\tau_i \mid \Theta^{(m)}, O_i) \right\} \]

\[ = \frac{\left\{ 1 - F_{T_1}(x_i) \right\} \alpha f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} \alpha f_{T_1}(x_i)}{\left\{ 1 - F_{T_1}(x_i) \right\} \alpha f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} \alpha f_{T_1}(x_i) + (1 - \alpha) f_{T_2}(x_i) \}
\[ \times \left\{ 1 - F_{T_1}(x_i) \right\} f_{T_2}(x_i) + \left\{ 1 - F_{T_2}(x_i) \right\} f_{T_1}(x_i) \]
\[ + 1 \cdot \left\{ 1 - E(\tau_i \mid \Theta^{(m)}, O_i) \right\} \]
Web Appendix B: Formulae for the First Term on the Right Hand Side of the Variance Estimator

The log-likelihood for \( \omega_j \) and \( \beta \) is given by:

\[
l_2(\beta, \omega \mid O_i) = \sum_{l \in A_j} \tau_l \zeta_l \exp(Z_l' \beta) \log(\omega_j) + \sum_{l \in A_j} (1 - \zeta_l) \log(1 - \omega_j \exp(Z_l' \beta)) \\
+ \sum_{l \in B_j} \log(1 - \omega_j \exp(Z_l' \beta)) \\
+ \sum_{l \in R_j - A_j - B_j} \exp(Z_l' \beta) \{ \tau_l \zeta_l - \zeta_l + \tau^*_l + I(\delta \neq 6) \} \log(\omega_j)
\]

The log-likelihood for \( \alpha \) is given by:

\[
l_1(\alpha \mid O_i) = \sum_{i \in \{i : \delta_i = 1\}} \{ \tau_i \zeta_i + (1 - \zeta_i) \} \log(\alpha_i) + \sum_{i \in \{i : \delta_i = 1\}} (1 - \tau_i) \zeta_i \log(1 - \alpha_i) \\
+ \sum_{i \in \{i : \delta_i = 2, 3\}} \log(\alpha_i) + \sum_{i \in \{i : \delta_i = 4, 5\}} \log(1 - \alpha_i) \\
+ \sum_{i \in \{i : \delta_i = 6\}} \tau^*_i \log(\alpha_i) + (1 - \tau^*_i) \log(1 - \alpha_i)
\]

Let \( \bar{\alpha} \) be the vector containing \((\alpha_0, \alpha_1)\). The components of the score function are:

\[
\frac{\partial l_2}{\partial \omega_j} = \sum_{l \in A_j} \frac{\tau_l \zeta_l \exp(Z_l' \beta)}{\omega_j} - \sum_{l \in A_j} \frac{(1 - \zeta_l) \exp(Z_l' \beta) \omega_j^{\exp(Z_l' \beta) - 1}}{1 - \omega_j^{\exp(Z_l' \beta)}} \\
- \sum_{l \in B_j} \frac{\exp(Z_l' \beta) \omega_j^{\exp(Z_l' \beta) - 1}}{1 - \omega_j^{\exp(Z_l' \beta)}} + \sum_{l \in R_j - A_j - B_j} \frac{\varphi_l \exp(z_l' \beta)}{\omega_j}
\]
\[
\frac{\partial^2}{\partial \beta^2} = \sum_{j=1}^{k} \sum_{l \in A_j} \tau_l \zeta_l Z_l \exp(Z'_l \beta) \log(\omega_j) - \sum_{l \in A_j} (1 - \zeta_l) \exp(Z'_l \beta) Z_l \log(\omega_j) \frac{\exp(Z'_l \beta)}{1 - \omega_j} \\
- \sum_{l \in B_j} \frac{\exp(Z'_l \beta) Z_l \log(\omega_j) \exp(Z'_l \beta)}{1 - \omega_j} \\
+ \sum_{l \in R_j - A_j - B_j} \{\tau_l \zeta_l - \zeta_l + \tau_l^* + I(\delta \neq 6)\} Z_l \exp(Z'_l \beta) \log(\omega_j)
\]

\[
\frac{\partial^1}{\partial \alpha_0} = \sum_{i \in \{i : \delta_i = 1\}} \{\tau_i \zeta_i + (1 - \zeta_i)\} \{1 - \frac{\exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}\} - \sum_{i \in \{i : \delta_i = 1\}} (1 - \tau_i) \zeta_i \exp(Z'_i \bar{\alpha}) \\
+ \sum_{i \in \{i : \delta_i \in \{2,3\}\}} \{1 - \frac{\exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}\} - \sum_{i \in \{i : \delta_i \in \{4,5\}\}} \exp(Z'_i \bar{\alpha}) \\
+ \sum_{i \in \{i : \delta_i = 6\}} \tau_i^* \{1 - \frac{\exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}\} - \frac{(1 - \tau_i^*) \exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}
\]

\[
\frac{\partial^1}{\partial \alpha_1} = \sum_{i \in \{i : \delta_i = 1\}} \{\tau_i \zeta_i + (1 - \zeta_i)\} Z_i \{1 - \frac{\exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}\} \\
- \sum_{i \in \{i : \delta_i = 1\}} \frac{(1 - \tau_i) \zeta_i Z_i \exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})} \\
+ \sum_{i \in \{i : \delta_i \in \{2,3\}\}} \{Z_i - \frac{Z_i \exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}\} - \sum_{i \in \{i : \delta_i \in \{4,5\}\}} \frac{Z_i \exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})} \\
+ \sum_{i \in \{i : \delta_i = 6\}} \tau_i^* \{Z_i - \frac{Z_i \exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}\} - \frac{(1 - \tau_i^*) Z_i \exp(Z'_i \bar{\alpha})}{1 + \exp(Z'_i \bar{\alpha})}
\]

The components for \(\frac{\partial^2 \log L(\Theta | X_{obs} \cdot X_{mis})}{\partial \Theta^2}\) are:
\[
\frac{\partial^2 l_2}{\partial \omega_j^2} = \sum_{l \in A_j} \frac{-\tau l \zeta \exp(Z_l')}{\omega_j^2} - \sum_{l \in A_j} \frac{(1 - \zeta l) \exp(Z_l') \{\exp(Z_l') - 1\} \omega_j \exp(Z_l')}{1 - \omega_j \exp(Z_l')} - \sum_{l \in B_j} \frac{\exp(2Z_l') \omega_j^2 \exp(Z_l') - 2(1 - \zeta l)}{(1 - \omega_j \exp(Z_l'))^2} - \sum_{l \in B_j} \frac{\exp(Z_l') \{\exp(Z_l') - 1\} \omega_j^2 \exp(Z_l')}{1 - \omega_j \exp(Z_l')} - \sum_{l \in B_j} \frac{\exp(2Z_l') \omega_j^2 \exp(Z_l') - 2}{(1 - \omega_j \exp(Z_l'))^2} + \sum_{l \in R_j - A_j - B_j} \frac{-\varphi l \exp(z_l')}{\omega_j^2}
\]

\[
\frac{\partial^2 l_2}{\partial \beta^2} = \sum_{j=1}^k \sum_{l \in A_j} \eta l \zeta l Z_l Z_l \log(\omega_j) \exp(Z_l') - \sum_{l \in A_j} (1 - \zeta l) \log^2(\omega_j) Z_l^2 \frac{\exp(2Z_l') \omega_j \exp(Z_l')}{1 - \omega_j \exp(Z_l')} - \sum_{l \in A_j} (1 - \zeta l) \log(\omega_j) Z_l^2 \frac{\omega_j \exp(Z_l') \exp(Z_l')}{1 - \omega_j \exp(Z_l')} - \sum_{l \in A_j} (1 - \zeta l) \log(\omega_j) Z_l^2 \frac{\omega_j \exp(Z_l') \exp(Z_l')}{(1 - \omega_j \exp(Z_l'))^2} - \sum_{l \in B_j} \frac{\log(\omega_j) Z_l \{\exp(2Z_l') \omega_j \exp(Z_l') - \exp(Z_l') \log(\omega_j) + Z_l \omega_j \exp(Z_l') \exp(Z_l')\}}{1 - \omega_j \exp(Z_l')} - \sum_{l \in B_j} \frac{\log^2(\omega_j) Z_l^2 \omega_j \exp(2Z_l') \exp(Z_l')}{(1 - \omega_j \exp(Z_l'))^2} + \sum_{l \in R_j - A_j - B_j} \varphi l \log(\omega_j) Z_l Z_l \exp(Z_l')
\]

\[
\frac{\partial^2 l_1}{\partial \alpha_0^2} = \sum_{i \in \{i; \delta_i = 1\}} \frac{-\{\tau_i l + (1 - \zeta l)\} \exp(Z_i' \alpha)}{1 + \exp(Z_i' \alpha)} - \sum_{i \in \{i; \delta_i = 1\}} \frac{(1 - \tau l) \zeta \exp(Z_i' \alpha)}{1 + \exp(Z_i' \alpha)} - \sum_{i \in \{i; \delta_i \in \{2,3\}\}} \frac{\exp(Z_i' \alpha)}{1 + \exp(Z_i' \alpha)} - \sum_{i \in \{i; \delta_i \in \{4,5\}\}} \frac{\exp(Z_i' \alpha)}{1 + \exp(Z_i' \alpha)} + \sum_{i \in \{i; \delta_i = 6\}} \frac{-\tau^* \exp(Z_i' \alpha)}{1 + \exp(Z_i' \alpha)} - \frac{(1 - \tau^* l) \exp(Z_i' \alpha)}{1 + \exp(Z_i' \alpha)}
\]
\[
\frac{\partial^2 l_1}{\partial \alpha^2_t} = \sum_{i \in \{i: \delta_i = 1\}} \frac{-\{\tau \zeta_i + (1 - \zeta_i)\} Z'_i Z_t \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2} - \sum_{i \in \{i: \delta_i = 1\}} \frac{(1 - \tau) \zeta_i Z'_i Z_t \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2}
\]
\[
- \sum_{i \in \{i: \delta_i \in \{2,3\}\}} \frac{Z'_i Z_t \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2} - \sum_{i \in \{i: \delta_i \in \{4,5\}\}} \frac{Z'_i Z_t \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2}
\]
\[
+ \sum_{i \in \{i: \delta_i = 6\}} \frac{-\tau^*_i Z'_i Z_t \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2} - \frac{(1 - \tau^*_i) Z'_i Z_t \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2}
\]

\[
\frac{\partial^2 l_1}{\partial \alpha_u \alpha_v} = \sum_{\delta = 1} \frac{-\{\tau \zeta_u + (1 - \zeta_u)\} Z'_u Z_v \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2} - \sum_{\delta = 1} \frac{(1 - \tau) \zeta_i Z'_i Z_u \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2}
\]
\[
- \sum_{\delta \in \{2,3\}} \frac{Z'_u Z_v \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2} - \sum_{\delta \in \{4,5\}} \frac{Z'_u Z_v \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2}
\]
\[
+ \sum_{\delta \in \{6\}} \frac{-\tau^*_i Z'_u Z_v \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2} - \frac{(1 - \tau^*_i) Z'_u Z_v \exp(Z'_i \bar{\alpha})}{\{1 + \exp(Z'_i \bar{\alpha})\}^2}
\]

\[
\frac{\partial^2 l_2}{\partial \omega_j \partial \beta} = \sum_{l \in A_j} \frac{\tau \zeta_l Z'_l \exp(Z'_l \beta)}{\omega_j}
\]
\[
+ \sum_{l \in A_j} (1 - \zeta_l) Z'_l \exp(Z'_l \beta) \frac{-\omega_j^{\exp(Z'_l \beta) - 1} - \log(\omega_j) \exp(Z'_l \beta) \omega_j^{\exp(Z'_l \beta) - 1}}{1 - \omega_j^{\exp(Z'_l \beta)}}
\]
\[
- \sum_{l \in A_j} (1 - \zeta_l) Z'_l \exp(Z'_l \beta) \frac{\exp(Z'_l \beta) \omega_j^{2 \exp(Z'_l \beta) - 1} \log(\omega_j)}{\{1 - \omega_j^{\exp(Z'_l \beta)}\}^2}
\]
\[
+ \sum_{l \in B_j} Z'_l \exp(Z'_l \beta) \frac{-\omega_j^{\exp(Z'_l \beta) - 1} - \log(\omega_j) \exp(Z'_l \beta) \omega_j^{\exp(Z'_l \beta) - 1}}{1 - \omega_j^{\exp(Z'_l \beta)}}
\]
\[
- \sum_{l \in B_j} Z'_l \exp(Z'_l \beta) \frac{\exp(Z'_l \beta) \omega_j^{2 \exp(Z'_l \beta) - 1} \log(\omega_j)}{\{1 - \omega_j^{\exp(Z'_l \beta)}\}^2}
\]
\[
+ \sum_{l \in R_j - A_j - B_j} \frac{(\tau \zeta_l - \zeta_l + \tau^*_i + 2) \exp(Z'_l \beta) Z'_l}{\omega_j}
\]

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E\left\{ \frac{\partial^2 \log L(\Theta | X_{\text{obs}}, X_{\text{miss}})}{\partial \Theta^2} \right\} \text{ can be calculated by replacing } \tau_l, \tau^*_l, \zeta_l, \tau_l \zeta_l \text{ by their expectations found in Equations 0.1-0.5 of this technical report.}

Web Appendix C: Likelihood Formation and Estimation Assuming a Semi-parametric Distribution for \( T_2 \)

If one would like to use a proportional hazards structure to model the hazard function for \( T_2 \), then the corresponding hazard function is

\[ \lambda(t_{2i} | Z_i) = \lambda_0(t_{2i}) \exp(Z'_i \eta) \]

where \( \eta \) represents the vector of regression parameters for the covariates \( Z_i \), and \( \lambda_0(t_{2i}) \) is defined as the baseline hazard function. Following reasoning similar to that proposed in Section 2.2 of the manuscript, we can let the \( q \) distinct failure times be represented by \( t_{2(1)} < \ldots < t_{2(q)} \). We assume a product-limit form for \( S_0(t_{2i}) \),

\[ S_0(t_{2i}) = \prod_{r: t_{2(r)} \leq t_{2i}} \varrho_r \]

where \( \varrho_r \geq 0, \varrho_0 = 1 \), \( S_0(t_{2(r)}) = S_0(t_{2(r-1)}) \), and \( \lambda(t_{2(r)} | Z_i) = 1 - \varrho_r^{\exp(Z'_i \eta)} \).

In the parameter estimation step it is then necessary to define \( \Omega \) as the set of parameters \( \varrho_1, \ldots, \varrho_q \), and \( \eta \) and \( L_3(\Omega | \mathcal{P}_i) \) can be rewritten in terms of the new distribution, specifically as

\[ L_3(\bar{\varrho}, \eta | \mathcal{P}_i) = \prod_{r=1}^{q} \prod_{l \in A_r} \varrho_r^{(1-\zeta_l) \exp(z'_l \eta)} (1 - \varrho_r^{\exp(z'_l \eta)}) \zeta_l \prod_{l \in B^*_r} (1 - \varrho_r^{\exp(z'_l \eta)}) \prod_{l \in R^*_r - A_r - B^*_r} \varrho_r^{\exp(z'_l \eta)} \]

where \( A_r \) is defined as the set of all subjects who experience a masked failure at time \( t(r) \), \( B^*_r \) represents the set of individuals who experience an unmasked failure attributable to \( T_2 \) at \( t(r) \) and \( R^*_r \) is the risk set at time \( t(r) \).
The E step takes the conditional expectation of the log-likelihood

\[ \log L(\Theta \mid X_{\text{obs}}, X_{\text{miss}}) = \log L_1(\Theta \mid X_{\text{obs}}, X_{\text{miss}}) + \log L_2(\Theta \mid X_{\text{obs}}, X_{\text{miss}}) + \log L_3(\Theta \mid X_{\text{obs}}, X_{\text{miss}}) \]

with respect to the distribution of the missing values of \( \tau_i \) and \( \zeta_i \), given \( X_{\text{obs}} \) and \( \Theta^{(m)} \), as defined in the manuscript. The expected values of \( \tau_i \), \( \zeta_i \) and \( \tau_i \zeta_i \) are provided in Appendix A.

The M step requires maximizing the expected complete data log-likelihood

\[ E_{X_{\text{miss}}}(\log L \mid X_{\text{obs}}, \Theta^{(m)}) = E_{X_{\text{miss}}}(\log L_1 \mid X_{\text{obs}}, \Theta^{(m)}) + E_{X_{\text{miss}}}(\log L_2 \mid X_{\text{obs}}, \Theta^{(m)}) + E_{X_{\text{miss}}}(\log L_3 \mid X_{\text{obs}}, \Theta^{(m)}) \]

with respect to \((\beta, \bar{\alpha}, \omega_1, \ldots, \omega_k, \eta, \varrho_1, \ldots, \varrho_q)\). We update \( \beta \) and \( \omega_1, \ldots, \omega_k \) by maximizing \( E_{X_{\text{miss}}}(\log L_2 \mid X_{\text{obs}}, \Theta^{(m)}) \), and we update \( \eta \) and \( \varrho_1, \ldots, \varrho_q \) by maximizing \( E_{X_{\text{miss}}}(\log L_3 \mid X_{\text{obs}}, \Theta^{(m)}) \).

Closed form solutions for each \( \varrho_r \) can be obtained given \( \eta \) if there are no ties at time \( t_{(r)} \). Without ties, and one event occurring in \( A_r \), it can be shown that the closed form solution for \( \varrho_r \) is

\[
\varrho_r = \left\{ \begin{array}{l}
1 - \frac{\zeta^*_{(r)} \exp(z_{(r)}' \eta)}{\exp(z_{(r)}' \eta) + \sum_{l \in R_r - A_r - B_r} \exp(z_{l}^r \eta)} \\
\text{exp}(-z_{(r)}' \eta)
\end{array} \right\},
\]

Without ties, and one event occurring in \( B_r^* \), it can also be shown that

\[
\varrho_r = \left\{ \begin{array}{l}
1 - \frac{\exp(z_{(r)}' \eta)}{\exp(z_{(r)}' \eta) + \sum_{l \in R_r - A_r - B_r} \exp(z_{l}^r \eta)} \\
\text{exp}(-z_{(r)}' \eta)
\end{array} \right\}.
\]

The subscript \((r)\) refers to the corresponding value of that variable for the single person who has an event at time \( t_{(r)} \), and \( \zeta^* \) indicates the conditional expectation of \( \zeta_{(r)} \) given the observed data and \( \Theta^{(m)} \). If there are ties, closed form solutions for
\( \varrho_r \) remain to be discovered, and the M step requires the joint estimation of \( \eta \) and \( \varrho_1, \ldots, \varrho_q \). Our approach for this is the same as the approach used in the manuscript for updating \( \beta \) and \( \omega_1, \ldots, \omega_k \).

For illustrative and comparative purposes, we fitted the model for the goserelin arm of the breast cancer trial data assuming a semiparametric distribution for \( T_2 \), and the graphical results are displayed below. Recall that in breast cancer example \( T_2 \) is interpreted as the age of natural menopause of premenopausal breast cancer patients undergoing adjuvant treatment. Formerly, we had assumed a normal distribution for this random variable. We released the normality assumption and fitted the semiparametric model to the goserelin arm alone without adjusting for covariates. That is, we assumed that 

\[
S(t_{2i}) = \prod_{r:t_{2(r)} \leq t_{2i}} \varrho_r.
\]

These data do not have ties, thus these results stem from the closed-form solutions for \( \varrho_r \).

Figures 1 and 2 display the graphical comparisons of the analysis results when assuming the product-limit survival function for \( T_2 \) to the results obtained based on the parametric assumption for \( T_2 \) presented in Section 4 of the manuscript. Specifically, Figure 1 compares the survival curves for \( T_1 \), the time to TIA, for patients of age 45, Figure 2 compares the CDF for \( T_2 \) under both assumptions. There is no considerable difference in the survival distributions for either \( T_1 \) or \( T_2 \) using the parametric model for \( T_2 \) and using the product-limit survival function.

[Figure 1 about here.]

[Figure 2 about here.]
Captions from Figures in the Web-based Supplemental Report

Figure 1: Comparison of the estimated distribution of $T_1$ assuming parametric and semiparametric distributions for $T_2$.

Figure 2: Comparison of the estimated semiparametric distribution for $T_2$ to the parametric distribution.
Goserelin Arm, Age 45

Pr(TIA>1) vs. Time (months)

Parametric
Semiparametric
Comparison of Parametric and Semiparametric Distributions for T2

Estimated CDF

- Parametric
- Semiparametric

Age at Menopause