Supporting Information for Treatment-Specific Marginal Structural Cox Model for the Effect of Treatment Discontinuation

The supporting information includes the proof that (6) and (7) are unbiased estimating equations and tables for the application.

1 Proof that (6) and (7) are Unbiased Estimating Equations

In order to show that (6) and (7) are unbiased estimating equations, we need to show that
\[
E \left\{ \left[ \omega_{ai}(t)[dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \right. \right. \\
\left. \left. \omega_{ai}(t)Z_i(t)\right| dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt \right\} = 0. \tag{1}
\]

First we show that
\[
\frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(v)dv \\
+ \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)Y_i(t)dt] \theta_D(t) \\
= \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(t).
\]

Proof:
\[
\frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(v)dv \\
+ \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)Y_i(t)dt] \theta_D(t) \\
= \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(t) \\
+ \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(t) \\
= 0 + \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(t) \\
= \frac{1}{K_D\{V_i \mid H(t)\}}K_R\{t \mid H(t), Z_i(t)\} \pi_A(X_i) \int_{V_i}^t [dN_i(t) - \lambda_{ai}(t)\exp\{\beta_{ai}^T Z_i(t)\}Y_i(t)dt] \theta_D(t).
\]

In the above, the first equality holds because \exp\{\beta_{ai}^T Z_i(t)\} = 1 when \(V_i \leq t\) and \(\Gamma_{Vi} = 0\). The second equality holds because the expression is equal to 0 except when \(V_i = t\). This is because
\[ Y_i(t) = 0 \text{ when } V_i < t \text{ and } \Gamma_{V_i} = 0. \]

It follows, then, that the expression inside the expectation given in (1) can be written as

\[
\begin{align*}
&\left(1 \over Z_{V_i}(t)\right) \frac{1}{f_D(V_i)} 1(\Gamma_{V_i} = 1) 1(A_i = a) 1(S_i \geq t) \bar{\theta}_R(t) \theta_D(V_i) \\
&\quad + \left(1 \over K_D \{ V_i | \overline{H}(t) \} \right) K_R \{ t | \overline{H}(t), Z_{V_i}(t) \} \pi_A(X_i) \\
&\quad + \frac{1}{K_D \{ V_i | \overline{H}(t) \} K_R \{ t | \overline{H}(t), Z_{V_i}(t) \} \pi_A(X_i)} \int_{\overline{V}_i} \left(1 \over z_{\nu}(t)\right) [dN_i(t) - \lambda_{a0}(t) \exp\{\beta^T \nu Z_{\nu}(t)\} ] \\
&\quad \times Y_i(t) \, dt] \theta_D(\nu) d\nu \\
&\quad + \frac{1}{K_D \{ V_i | \overline{H}(t) \} K_R \{ t | \overline{H}(t), Z_{V_i}(t) \} \pi_A(X_i)} \int_{\overline{V}_i} \left(1 \over z_{\nu}(t)\right) [dN_i(t) - \lambda_{a0}(t) Y_i(t) \, dt].
\end{align*}
\]

Refer to (2) as “component 1”; refer to (3) as “component 2”; refer to (4) and (5) as “component 3”; and refer to (6) as “component 4”. We show that (1) holds by showing:

(i) The expectation of component 1 is equal to \( E \left[ \int_0^t \left(1 \over z_{\nu}(t)\right) 1(T_i > \nu) \, dM_i^{(a,\nu)}(t) \theta_D(\nu) \overline{\theta}_R(t) \, d\nu \right] \).

(ii) The expectation of component 2 is equal to \( E \left\{ 1(T_i > t) \left(1 \over 0\right) \, dM_i^{(a,t)}(t) \overline{\theta}_D(t) \overline{\theta}_R(t) \right\} \).

(iii) The expectation of component 3 is equal to \( E \left\{ \int_0^t 1(T_i \leq \nu) \left(1 \over z_{\nu}(t)\right) \, dM_i^{(a,\nu)}(t) \theta_D(\nu) \, d\nu \overline{\theta}_R(t) \right\} \).

(iv) The expectation of component 4 is equal to \( E \left[ 1(T_i \leq t) \left(1 \over 0\right) \, dM_i^{(a,t)}(t) \overline{\theta}_D(t) \overline{\theta}_R(t) \right] \).

In the proofs below, we use “NUC” to refer to the assumption of no unmeasured confounders.

We also use the following notation. Let

\[
F_i = \left\{ X_i, A_i, C_i, T_i, D_i, R_i, \overline{Q}_i(T_i), \overline{Z}_i(T_i), \left( D_i^{(a)}, T_i^{(a,\nu)}, R_i^{(a,\nu)}, \overline{Q}_i^{(a,\nu)}(T_i^{(a,\nu)}) : \nu < T_i^{(a,\infty)}, a \in \{0, 1\} \right) \right\}
\]

be the full set of potential variables, which contains all observed variables and potential outcomes for patient \( i \). Also, let

\[
F_{A_i} = \left\{ X_i, C_i, T_i, D_i, R_i, \overline{Q}_i(T_i), \overline{Z}_i(T_i), \left( D_i^{(a)}, T_i^{(a,\nu)}, R_i^{(a,\nu)}, \overline{Q}_i^{(a,\nu)}(T_i^{(a,\nu)}) : \nu < T_i^{(a,\infty)}, a \in \{0, 1\} \right) \right\},
\]

\[
F_{D_i} = \left\{ X_i, A_i, C_i, T_i, R_i, \overline{Q}_i(T_i), \overline{Z}_i(T_i), \left( T_i^{(a,\nu)}, R_i^{(a,\nu)}, \overline{Q}_i^{(a,\nu)}(T_i^{(a,\nu)}) : \nu < T_i^{(a,\infty)}, a \in \{0, 1\} \right) \right\},
\]

and

\[
F_{R_i} = \left\{ X_i, A_i, C_i, T_i, D_i, \overline{Q}_i(T_i), \overline{Z}_i(T_i), \left( D_i^{(a)}, T_i^{(a,\nu)}, \overline{Q}_i^{(a,\nu)}(T_i^{(a,\nu)}) : \nu < T_i^{(a,\infty)}, a \in \{0, 1\} \right) \right\}.
\]
Proof of (i)

\[
E\left\{ 1(A_i = a) \frac{1(V_i \leq t, \Gamma_{Vi} = 1)}{\pi_A(X_i)} f_D\{V_i \mid X_i, \mathcal{Q}(t), A_i = a\} \frac{1(S_i \geq t)}{K_R\{t \mid X_i, \mathcal{Q}_i(t), Z_{Vi}(t) = 1, A_i = a\}} \left( \frac{1}{Z_{Vi}(t)} \right) \right\} \\
\times [dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T Z_{Vi}(t)\} Y_i(t) dt] \theta_D(V_i) \bar{\theta}_R(t) \\
= E\left[ E\left\{ \frac{1(A_i = a)}{\pi_A(X_i)} \frac{1(V_i \leq t, \Gamma_{Vi} = 1)}{f_D\{V_i \mid X_i, \mathcal{Q}(t), A_i = a\}} \frac{1(R_i^{(a,D)}(a)) \geq t)}{K_R\{t \mid X_i, \mathcal{Q}_i(t), Z_{Vi}(t) = 1, A_i = a\}} \left( \frac{1}{Z_{Vi}(t)} \right) \right\} \\
\times \theta_D(V_i) \bar{\theta}_R(t) \right\} \text{ by consistency} \\
= E\left[ \frac{1(A_i = a)}{\pi_A(X_i)} \frac{1(V_i \leq t, \Gamma_{Vi} = 1)}{f_D\{V_i \mid X_i, \mathcal{Q}(t), A_i = a\}} \left( \frac{1}{Z_{Vi}(t)} \right) \right]\left[ dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T Z_{Vi}(t)\} Y_i(t) dt \right] \\
\times \theta_D(V_i) \bar{\theta}_R(t) \text{ by NUC and consistency} \\
= E\left[ \frac{1(A_i = a)}{\pi_A(X_i)} \frac{1(V_i \leq t, \Gamma_{Vi} = 1)}{f_D\{V_i \mid X_i, \mathcal{Q}(t), A_i = a\}} \left( \frac{1}{Z_{Vi}(t)} \right) \right]\left[ dN_i^{(a,V_i)}(t) - \lambda_{a0}(t)\exp\{\beta_a^T Z_{Vi}(t)\} Y_i^{(a,V_i)}(t) dt \right] \\
\times \theta_D(V_i) \bar{\theta}_R(t) \mid F_{Ai} \right\} \text{ by consistency} \\
= E\left[ \frac{1(A_i = a)}{\pi_A(X_i)} \frac{1(D^{(a)} \leq t)}{f_D\{D_i^{(a)} \mid X_i, \mathcal{Q}(t), A_i = a\}} \left( \frac{1}{Z_{D_i^{(a)}(t)}} \right) \left[ dM_i^{(a,D_i^{(a)})(a)}(t) \theta_D(D_i^{(a)}) \bar{\theta}_R(t) \right] \\
\text{ by consistency} \\
= E\left[ \frac{1(D^{(a)} \leq t)}{f_D\{D_i^{(a)} \mid X_i, \mathcal{Q}(t), A_i = a\}} \left( \frac{1}{Z_{D_i^{(a)}(t)}} \right) \left[ dM_i^{(a,D_i^{(a)})(a)}(t) \theta_D(D_i^{(a)}) \bar{\theta}_R(t) \right] \right\} \text{ by NUC} \\
= E\left[ \frac{1(V_i \leq t, \Gamma_{Vi} = 1)}{f_D\{V_i \mid X_i, \mathcal{Q}(t), A_i = a\}} \left( \frac{1}{Z_{Vi}(t)} \right) \right]\left[ dM_i^{(a,V_i)}(t) \theta_D(V_i) \bar{\theta}_R(t) \right] \mid F_{Di}, A_i = a \right\} \\
\text{ by consistency and NUC} \\
= E\left[ \int_0^t \left( \frac{1}{z_{Vi}(t)} \right) \frac{P\{V_i \in (\nu, \nu + dv), \Gamma_{Vi} = 1 \mid X_i, \mathcal{Q}(t), A_i = a\} dM_i^{(a,D_i^{(a)})(a)}(t) \theta_D(D_i^{(a)}) \bar{\theta}_R(t) \right] \right\} \text{ by NUC} \\
= E\left[ \int_0^t \left( \frac{1}{z_{Vi}(t)} \right) \frac{1(T_i > v)}{f_D\{V_i \mid X_i, \mathcal{Q}(t), A_i = a\}} dM_i^{(a,v)}(t) \theta_D(D_i^{(a)}) \bar{\theta}_R(t) dv \right] \\
= E\left[ \int_0^t \left( \frac{1}{z_{Vi}(t)} \right) 1(T_i > v) dM_i^{(a,v)}(t) \theta_D(D_i^{(a)}) \bar{\theta}_R(t) dv \right].
Proof of (ii)

\[ E \left\{ 1(V_i > t)1(A_i = a)1(S_i \geq t) \left( \begin{array}{c} 1 \\ 0 \end{array} \right) [dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T \times 0\}Y_i(t)dt] \right. \]

\[ \left. \frac{\overline{\theta}_D(t)}{K_D\{t \mid X_i, \overline{Q}_i(t), A_i = a\}} \right\} \]

\[ = E \left[ E \left\{ 1(V_i > t)1(A_i = a)1(R_i^{(a,D^{(a)*})} \geq t) \left( \begin{array}{c} 1 \\ 0 \end{array} \right) [dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T \times 0\}Y_i(t)dt] \right. \right. \]

\[ \times \frac{\overline{\theta}_D(t)}{K_D\{t \mid X_i, \overline{Q}_i(t), A_i = a\}} \frac{1}{\pi_A(X_i)} \left. \right\} \text{ by consistency} \]

\[ = E \left[ 1(V_i > t)1(A_i = a) \left( \frac{1}{\pi_A(X_i)} \right) \left( \begin{array}{c} 1 \\ 0 \end{array} \right) [dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T \times 0\}Y_i(t)dt] \right. \]

\[ \left. \frac{\overline{\theta}_D(t)\overline{\theta}_R(t)}{K_D\{t \mid X_i, \overline{Q}_i(t), A_i = a\}} \right\} \text{ by consistency} \]

\[ = E \left[ 1(V_i > t)1(A_i = a) \left( \frac{1}{\pi_A(X_i)} \right) \left( \begin{array}{c} 1 \\ 0 \end{array} \right) [dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T \times 0\}Y_i^{(a,t)}(t)dt] \right. \]

\[ \times \frac{\overline{\theta}_D(t)\overline{\theta}_R(t)}{K_D\{t \mid X_i, \overline{Q}_i(t), A_i = a\}} \right\} \text{ by NUC and consistency} \]

Proof of (iii)

\[ E \left\{ 1(V_i \leq t, \Gamma_{V_i} = 0)1(A_i = a)1(S_i \geq t) \left( \begin{array}{c} 1 \\ 0 \end{array} \right) \int_{\Gamma_{V_i}}^{t} \left( \begin{array}{c} 1 \\ z_\nu(t) \end{array} \right) [dN_i(t) - \lambda_{a_\nu}(t)\exp\{\beta_a^T z_\nu(t)\}Y_i(t)dt] \right. \]

\[ \times \frac{\overline{\theta}_R(t)}{K_R\{t \mid X_i, \overline{Q}_i(t), Z_{V_i}(t) = 0, A_i = a\}} \frac{1}{\pi_A(X_i)} \right\} \]
\[
\begin{align*}
&= E \left[ E \left( \frac{1(V_i \leq t, \Gamma_{V_i} = 0)1(A_i = a)1(R_i^{(a,D)}) \geq t}{K_D(V_i \mid X_i, \overline{Q}_i(t), A_i = a) \frac{\bar{\theta}_R(t)}{K_R(t \mid X_i, \overline{Q}_i(t), Z_{V_i}(t) = 0, A_i = a) \frac{1}{\pi_A(X_i)}}} \right) \int_{V_i}^{t} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\}Y_i(t)dt \right] \\
&\times \theta_D(\nu) d\nu \right] \left( \frac{1(R_i^{(a,D)}) \geq t}{K_R(t \mid X_i, \overline{Q}_i(t), Z_{V_i}(t) = 0, A_i = a) \frac{1}{\pi_A(X_i)} | F_{R_i}} \right) \right] \text{ by consistency}
\end{align*}
\]

\[
\begin{align*}
&= E \left[ \frac{1(V_i \leq t, \Gamma_{V_i} = 0)1(A_i = a)}{K_D(V_i \mid X_i, \overline{Q}_i(t), A_i = a) \frac{\bar{\theta}_R(t)1(A_i = a)}{\pi_A(X_i)}} \int_{V_i}^{t} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\}Y_i(t)dt \right] \\
&\times \theta_D(\nu) d\nu \right] \left( \frac{1(R_i^{(a,D)}) \geq t}{K_R(t \mid X_i, \overline{Q}_i(t), Z_{V_i}(t) = 0, A_i = a) \frac{1}{\pi_A(X_i)} | F_{R_i}, A_i = a} \right) \text{ by NUC}
\end{align*}
\]

\[
\begin{align*}
&= E \left[ \frac{\bar{\theta}_R(t)1(A_i = a)}{\pi_A(X_i)} \int_{0}^{t} \frac{1(V_i \leq \nu, \Gamma_{V_i} = 0)}{K_D(V_i \mid X_i, \overline{Q}_i(t), A_i = a)} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\} \right] \\
&\times Y_i(t) dt | \theta_D(\nu) d\nu \right] \\
&= E \left[ \frac{\bar{\theta}_R(t)1(A_i = a)}{\pi_A(X_i)} \int_{0}^{t} \frac{1(T_i \leq \nu, \Gamma_{V_i} = 0)}{K_D(T_i \mid X_i, \overline{Q}_i(t), A_i = a)} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i^{(a,\nu)}(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\} \right] \\
&\times Y_i^{(a,\nu)}(t) dt | \theta_D(\nu) d\nu \right] \\
&= E \left[ \frac{\bar{\theta}_R(t)1(A_i = a)}{\pi_A(X_i)} \int_{0}^{t} \frac{1(T_i^{(a,\infty)} \leq \nu, 1(D_i^{(a)} > T_i^{(a,\infty)})}{K_D(T_i^{(a,\infty)} \mid X_i, \overline{Q}_i(t), A_i = a)} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i^{(a,\nu)}(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\} \right] \\
&\times Y_i^{(a,\nu)}(t) dt | \theta_D(\nu) d\nu | F_{A_i} \right] \\
&= E \left[ \frac{\bar{\theta}_R(t)1(A_i = a)}{\pi_A(X_i)} \int_{0}^{t} \frac{1(T_i^{(a,\infty)} \leq \nu, 1(D_i^{(a)} > T_i^{(a,\infty)})}{K_D(T_i^{(a,\infty)} \mid X_i, \overline{Q}_i(t), A_i = a)} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i^{(a,\nu)}(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\} \right] \\
&\times Y_i^{(a,\nu)}(t) dt | \theta_D(\nu) d\nu | F_{A_i} \right] \\
&= E \left[ \frac{1(A_i = a)}{\pi_A(X_i)} \bar{\theta}_R(t) \int_{0}^{t} \frac{1(T_i^{(a,\infty)} \leq \nu, 1(D_i^{(a)} > T_i^{(a,\infty)})}{K_D(T_i^{(a,\infty)} \mid X_i, \overline{Q}_i(t), A_i = a)} \left( \frac{1}{z_{\nu}(t)} \right) \left[ dN_i^{(a,\nu)}(t) - \lambda_{a0}(t)\exp\{\beta_a^T z_{\nu}(t)\} \right] \\
&\times Y_i^{(a,\nu)}(t) dt | \theta_D(\nu) d\nu | F_{D_i, A_i = a} \right] \text{ by NUC}
\end{align*}
\]
\[
E \left[ \frac{1}{K_D \{ T_i | X_i, Q_i(t), A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) dM^{(a,\nu)}_i \theta_D(\nu) d\nu \mid F_{D_i}, A_i = a \right]
\]

by consistency

\[
E \left[ \Theta_R(t) \int_0^t \left( \begin{array}{c} 1 \\
\end{array} \right) 1(T_i \leq \nu) dM^{(a,\nu)}_i \theta_D(\nu) d\nu E \left[ \frac{1}{K_D \{ T_i | X_i, Q_i(t), A_i = a \}} \left( \begin{array}{c} 1(D_i > T_i) \\
\end{array} \right) \mid F_{D_i}, A_i = a \right] \right]
\]

by consistency

\[
E \left\{ \int_0^1 1(T_i \leq \nu) \left( \begin{array}{c} 1 \\
\end{array} \right) dM^{(a,\nu)}_i \theta_D(\nu) d\nu \theta_R(t) \right\}
\]

by NUC.

In the above, the fifth equality holds because \( dN^{(a)}(t) = dN_i(t) \) and \( Y^{(a)}(t) = Y_i(t) \) for \( \nu \geq T_i \).

**Proof of (iv)**

\[
E \left\{ \frac{1(1(V \leq t, \Gamma_Y = 0) 1(1(A_i = a) 1(S_i \geq t))}{K_D \{ V | X_i, Q_i(t), A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) \left[ dN_i(t) - \lambda a(t) \exp \{ \beta^T_a \times 0 \} Y_i(t) dt \right] \theta_D(t) \right\}
\]

\[
\times \frac{1}{K_R \{ t | X_i, Q_i(t), V_i(t) = 0, A_i = a \}} \pi_A(X_i) \right\}
\]

\[
E \left[ \frac{1(1(V \leq t, \Gamma_Y = 0) 1(1(A_i = a) 1(R^{(a,D)}_i \geq t))}{K_D \{ V | X_i, Q_i, A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) \left[ dN_i(t) - \lambda a(t) \exp \{ \beta^T_a \times 0 \} Y_i(t) dt \right] \theta_D(t) \theta_R(t) \right]
\]

\[
\times \frac{1}{K_R \{ t | X_i, Q_i(t), V_i(t) = 0, A_i = a \}} \pi_A(X_i) \right\}
\]

by NUC

\[
E \left[ \frac{1(1(V \leq t, \Gamma_Y = 0) 1(1(A_i = a) 1(R^{(a,D)}_i \geq t))}{K_D \{ V | X_i, Q_i, A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) \left[ dN_i(t) - \lambda a(t) \exp \{ \beta^T_a \times 0 \} Y_i(t) dt \right] \theta_D(t) \theta_R(t) \right]
\]

by NUC and consistency

\[
E \left[ \frac{1(1(V \leq t, \Gamma_Y = 0) 1(1(A_i = a) 1(R^{(a,D)}_i \geq t))}{K_D \{ V | X_i, Q_i, A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) \left[ dN_i(t) - \lambda a(t) \exp \{ \beta^T_a \times 0 \} Y_i(t) dt \right] \theta_D(t) \theta_R(t) \right]
\]

by consistency

\[
E \left[ \frac{1(1(V \leq t, \Gamma_Y = 0) 1(1(A_i = a) 1(R^{(a,D)}_i \geq t))}{K_D \{ V | X_i, Q_i, A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) \left[ dN_i(t) - \lambda a(t) \exp \{ \beta^T_a \times 0 \} Y_i(t) dt \right] \theta_D(t) \theta_R(t) \right]
\]

by NUC

\[
E \left[ \frac{1(1(V \leq t, \Gamma_Y = 0) 1(1(A_i = a) 1(R^{(a,D)}_i \geq t))}{K_D \{ V | X_i, Q_i, A_i = a \}} \left( \begin{array}{c} 1 \\
\end{array} \right) \left[ dN_i(t) - \lambda a(t) \exp \{ \beta^T_a \times 0 \} Y_i(t) dt \right] \theta_D(t) \theta_R(t) \right]
\]

by consistency
By (i)-(iv), it is clear that
\begin{align*}
  & E \left\{ \frac{\omega \alpha(t)}{\omega \alpha(t)} dN(t) - \lambda_0(t) \exp \left( \beta ZV_i(t) \right) Y(t) dt \right\} \\
  & = E \left\{ \int_0^t \left( \frac{1}{z(v)} \right) 1(T_i > v) dM^{(a,v)}(t) \theta_D(v) \bar{Y}_R(t) dv \right\} + E \left\{ 1(T_i > t) \left( \frac{1}{0} \right) dM^{(a,t)}(t) \bar{Y}_D(t) \bar{Y}_R(t) \right\} \\
  & + E \left\{ \int_0^t \left( \frac{1}{z(v)} \right) 1(T_i \leq v) dM^{(a,v)}(t) \theta_D(v) dv \bar{Y}_R(t) \right\} + E \left\{ 1(T_i \leq t) \left( \frac{1}{0} \right) dM^{(a,t)}(t) \bar{Y}_D(t) \bar{Y}_R(t) \right\} \\
  & = E \left\{ \int_0^t \left( \frac{1}{z(v)} \right) dM^{(a,v)}(t) \theta_D(v) \bar{Y}_R(t) dv \right\} + E \left\{ 1(0) \right\} dM^{(a,t)}(t) \bar{Y}_D(t) \bar{Y}_R(t) \right\} \\
  & = \left( 0 \right) + \left( 0 \right) = \left( 0 \right) .
\end{align*}
Therefore, (6) and (7) are unbiased estimating equations for $\beta_a$ and $\Lambda_0$.

## 2 Tables

**Table S1:** Baseline summary table for covariates considered in the GARFIELD-AF data application. The categorical covariate “Country” is not included in the table even though it is considered in the analysis, since there are 35 levels of this variable. “IQR” stands for interquartile range; “AC clinic” stands for anticoagulation clinic; “TIA” stands for transient ischemic attack; “VKA” stands for vitamin K antagonist; “NOAC” stands for non vitamin K oral anticoagulant.

| Baseline characteristics                  | Patients that discontinued (n = 3114) | Patients that did not discontinue (n = 20768) |
|-------------------------------------------|--------------------------------------|-----------------------------------------------|
| Violated the regime (%)                   | 1437 (46.15)                         | 1663 (8.01)                                   |
| Violated the regime prior                 | 212 (6.81)                           | 1663 (8.01)                                   |
| to/at discontinuation (%)                 | 1827 (58.67)                         | 11307 (54.44)                                 |
| Male (%)                                  | 70 (61.78)                           | 72 (64.79)                                    |
| Age, median (IQR)                         | 1032 (33.14)                         | 5257 (25.31)                                  |
| < 65 years (%)                            | 984 (31.60)                          | 7249 (34.90)                                  |
| 65-74 years (%)                           | 1098 (35.26)                         | 8262 (39.78)                                  |
| 75 years (%)                              |                                      |                                               |
| Race                                      |                                      |                                               |
| Caucasian (%)                             | 2235 (71.77)                         | 13221 (63.66)                                 |
| Hispanic/Latino (%)                       | 120 (3.85)                           | 1321 (6.36)                                   |
| Afro-Caribbean (%)                        | 10 (0.32)                            | 131 (0.63)                                    |
| Asian (not Chinese) (%)                   | 553 (17.76)                          | 4796 (23.09)                                  |
| Chinese (%)                               | 51 (1.64)                            | 504 (2.43)                                    |
| Mixed/Other                               |                                      |                                               |
| /Unwilling to declare (%)                 | 145 (4.66)                           | 795 (3.83)                                    |
| Body mass index, median (IQR)             | 27 (24.31)                           | 27 (24.31)                                    |
| Missing (% missing)                       | 677 (21.74)                          | 4599 (22.14)                                  |
| Hypertension (%                           | 2377 (76.33)                         | 16159 (77.81)                                 |
| No (%)                                    | 728 (23.38)                          | 4540 (21.86)                                  |

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Table S1 – Continued from previous page

| Baseline characteristics                  | Patients that discontinued (n = 3114) | Patients that did not discontinue (n = 20768) |
|-------------------------------------------|---------------------------------------|-----------------------------------------------|
| Unknown (%)                               | 9 (0.29)                              | 69 (0.33)                                     |
| Patients with diabetes (%)                | 649 (20.84)                           | 4901 (23.6)                                   |
| Smoking                                   |                                       |                                               |
| Never smoked (%)                          | 1820 (58.45)                          | 12356 (59.50)                                 |
| Ex-smoker (%)                             | 749 (24.05)                           | 4675 (22.51)                                  |
| Current smoker (%)                        | 305 (9.79)                            | 1920 (9.24)                                   |
| Unknown (%)                               | 240 (7.71)                            | 1817 (8.75)                                   |
| Alcohol consumption                       |                                       |                                               |
| Abstinent/light (%)                       | 2236 (71.80)                          | 15442 (74.35)                                 |
| Moderate/heavy (%)                        | 370 (11.88)                           | 2024 (9.75)                                   |
| Unknown (%)                               | 508 (16.31)                           | 3302 (15.90)                                  |
| Type of atrial fibrillation               |                                       |                                               |
| Permanent (%)                             | 283 (9.09)                            | 3004 (14.46)                                  |
| Persistent (%)                            | 504 (16.18)                           | 3507 (16.89)                                  |
| Paroxysmal (%)                            | 879 (28.23)                           | 5565 (26.80)                                  |
| New (%)                                   | 1448 (46.50)                          | 8692 (41.85)                                  |
| Care setting at diagnosis                 |                                       |                                               |
| Hospital (%)                              | 1719 (55.20)                          | 10935 (52.65)                                 |
| Office (%)                                | 969 (31.12)                           | 7582 (36.51)                                  |
| AC clinic/thrombosis centre (%)           | 9 (0.29)                              | 99 (0.48)                                     |
| Emergency room (%)                        | 417 (13.39)                           | 2152 (10.36)                                  |
| Heart failure (%)                         | 684 (21.97)                           | 4650 (22.39)                                  |
| Coronary artery disease (%)               | 672 (21.58)                           | 4205 (20.25)                                  |
| Stroke/TIA (%)                            | 287 (9.22)                            | 2485 (11.97)                                  |
| Systemic embolization                     |                                       |                                               |
| Yes (%)                                   | 16 (0.51)                             | 174 (0.84)                                    |
| No (%)                                    | 3078 (98.84)                          | 20456 (98.50)                                 |
| Unknown (%)                               | 20 (0.64)                             | 138 (0.66)                                    |
| Bleeding history                          |                                       |                                               |
| Yes (%)                                   | 88 (2.83)                             | 338 (1.63)                                    |
| No (%)                                    | 3009 (96.63)                          | 20341 (97.94)                                 |
| Unknown (%)                               | 17 (0.55)                             | 89 (0.43)                                     |
| Chronic kidney disease                    |                                       |                                               |
| Stage 1-2 (%)                             | 558 (17.92)                           | 3445 (16.59)                                  |
| Stage 3-5 (%)                             | 416 (13.36)                           | 2198 (10.58)                                  |
| None (%)                                  | 2034 (65.32)                          | 14159 (68.18)                                 |
| Unknown (%)                               | 106 (3.40)                            | 966 (4.65)                                    |
| Acute coronary syndrome                   |                                       |                                               |
| Yes (%)                                   | 324 (10.40)                           | 2152 (10.36)                                  |
| No (%)                                    | 2774 (89.08)                          | 18523 (89.19)                                 |
| Unknown (%)                               | 16 (0.51)                             | 93 (0.45)                                     |
| Region                                    |                                       |                                               |
| Asia (%)                                  | 587 (18.85)                           | 5073 (24.43)                                  |
| Europe (%)                                | 2018 (64.80)                          | 12142 (58.46)                                 |
| Latin America (%)                         | 149 (4.78)                            | 1621 (7.81)                                   |
| North America (%)                         | 152 (4.88)                            | 776 (3.74)                                    |
| Rest of world (%)                         | 208 (6.68)                            | 1156 (5.57)                                   |
| Type of insurance                         |                                       |                                               |
| Combination (%)                           | 340 (10.92)                           | 1805 (8.69)                                   |
| Private (insurance) (%)                   | 196 (6.29)                            | 1343 (6.47)                                   |
| Private (out of pocket) (%)               | 73 (2.34)                             | 832 (4.01)                                    |
| Public insurance (%)                      | 2538 (75.72)                          | 15688 (75.54)                                 |
| Unknown (%)                               | 147 (4.72)                            | 1100 (5.30)                                   |
| Care setting specialty                    |                                       |                                               |
| Cardiology (%)                            | 2033 (65.29)                          | 13982 (67.32)                                 |
| Geriatrics (%)                            | 7 (0.22)                              | 67 (0.32)                                     |
| Internal medicine (%)                     | 558 (17.92)                           | 3566 (17.17)                                  |
| Neurology (%)                             | 33 (1.06)                             | 333 (1.60)                                    |
| Primary care/general practice (%)         | 483 (15.51)                           | 2820 (13.58)                                  |
| Dementia                                  |                                       |                                               |
| Yes (%)                                   | 36 (1.16)                             | 293 (1.41)                                    |
| No (%)                                    | 3061 (98.30)                          | 20351 (97.99)                                 |
| Unknown (%)                               | 17 (0.55)                             | 124 (0.60)                                    |
| Sector in which patient is treated        |                                       |                                               |
| Private sector (%)                        | 842 (27.04)                           | 6018 (28.98)                                  |

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Table S1 – Continued from previous page

| Baseline characteristics               | Patients that discontinued (n = 3114) | Patients that did not discontinue (n = 20768) |
|----------------------------------------|---------------------------------------|---------------------------------------------|
| Public sector (%)                      | 2246 (72.13)                          | 14583 (70.22)                               |
| Unknown (%)                            | 26 (0.83)                             | 167 (0.80)                                  |
| Weeks from onset to treatment, median (IQR) | 1.20 (0.40, 3.00)                     | 1.5 (0.50, 3.20)                            |
| Missing (% missing)                    | 734 (23.57)                           | 5821 (28.03)                                |
| Pulse (IQR)                            | 87 (72, 110)                          | 85 (72, 105)                                |
| Missing (% missing)                    | 189 (6.07)                            | 1279 (6.16)                                 |
| Systolic blood pressure in mm Hg (IQR) | 132 (120,144.2)                       | 132 (120, 145)                              |
| Missing (% missing)                    | 182 (5.84)                            | 1204 (5.80)                                 |
| Diastolic blood pressure in mm Hg (IQR)| 80 (70,90)                            | 80 (70, 89)                                 |
| Missing (% missing)                    | 182 (5.84)                            | 1204 (5.80)                                 |
| Height in cm. (IQR)                    | 168 (161, 176)                        | 167 (160, 174)                              |
| Missing (% missing)                    | 677 (21.74)                           | 4599 (22.14)                                |
| Weight in kg. (IQR)                    | 72 (57, 83)                           | 70 (57, 82)                                 |
| Missing (% missing)                    | 677 (21.74)                           | 4599 (22.14)                                |
| Baseline treatment                     |                                       |                                             |
| VKA (%)                                | 1511 (48.52)                          | 10397 (50.06)                               |
| NOAC(%)                                | 1603 (51.48)                          | 10371 (49.94)                               |
**Table S2:** Results from fitting the MSM for the treatment-specific effect of discontinuation to the GARFIELD-AF data. Results are based on the 30 day definition of discontinuation. “Param.” stands for parameter; “Coef.” contains the coefficient estimate for the corresponding parameter; “SE” stands for standard error; “SE∗” stands for systemic embolism; “MI” stands for myocardial infarction.

| Endpoint                  | Param. | Coef. | exp(Coef.) | Robust SE | Pvalue |
|---------------------------|--------|-------|------------|-----------|--------|
| Death                     | β¹*    | -0.31 | 0.73       | 0.07      | < 0.001|
|                           | β²*    | 0.27  | 1.31       | 0.18      | 0.137  |
|                           | β³*    | 0.09  | 1.10       | 0.30      | 0.756  |
| Cardiovascular Death      | β¹*    | -0.46 | 0.63       | 0.12      | < 0.001|
|                           | β²*    | 0.18  | 1.20       | 0.35      | 0.612  |
|                           | β³*    | 0.20  | 1.23       | 0.68      | 0.766  |
| Stroke/SE*                | β¹*    | -0.24 | 0.79       | 0.17      | 0.168  |
|                           | β²*    | 0.54  | 1.71       | 0.33      | 0.102  |
|                           | β³*    | 0.35  | 1.41       | 0.47      | 0.465  |
| MI                        | β¹*    | -0.13 | 0.88       | 0.16      | 0.433  |
|                           | β²*    | 0.43  | 1.54       | 0.43      | 0.320  |
|                           | β³*    | 0.09  | 1.09       | 0.58      | 0.875  |
| Death/Stroke/SE*          | β¹*    | -0.30 | 0.74       | 0.07      | < 0.001|
|                           | β²*    | 0.30  | 1.35       | 0.17      | 0.070  |
|                           | β³*    | 0.15  | 1.17       | 0.26      | 0.559  |
| Death/Stroke/SE*/MI       | β¹*    | -0.28 | 0.75       | 0.06      | < 0.001|
|                           | β²*    | 0.33  | 1.39       | 0.16      | 0.036  |
|                           | β³*    | 0.11  | 1.12       | 0.25      | 0.660  |
Table S3: Results from fitting the MSM for the constant effect of discontinuation to the GARFIELD-AF data. Results are based on the 30 day definition of discontinuation. “Param.” stands for parameter; “Coef.” contains the coefficient estimate for the corresponding parameter; “SE” stands for standard error; “SE*” stands for systemic embolism; “MI” stands for myocardial infarction.

| Endpoint                  | Param. | Coef. | exp(Coef.) | Robust SE | Pvalue   |
|---------------------------|--------|-------|------------|-----------|----------|
| Death                     |        |       |            |           |          |
| 1                        | $\beta^{1*}$ | -0.31 | 0.74       | 0.07      | < 0.001  |
|                           | $\beta^{2*}$ | 0.31  | 1.37       | 0.15      | 0.032    |
| Cardiovascular Death      |        |       |            |           |          |
| Stroke/SE*                |        |       |            |           |          |
|                           | $\beta^{1*}$ | -0.45 | 0.64       | 0.13      | < 0.001  |
|                           | $\beta^{2*}$ | 0.26  | 1.30       | 0.32      | 0.410    |
| MI                        |        |       |            |           |          |
|                           | $\beta^{1*}$ | -0.12 | 0.89       | 0.16      | 0.215    |
|                           | $\beta^{2*}$ | 0.47  | 1.60       | 0.29      | 0.107    |
| Death/Stroke/SE*          |        |       |            |           |          |
|                           | $\beta^{1*}$ | -0.29 | 0.75       | 0.06      | < 0.001  |
|                           | $\beta^{2*}$ | 0.37  | 1.45       | 0.13      | 0.004    |
| Death/Stroke/SE*/MI       |        |       |            |           |          |
|                           | $\beta^{1*}$ | -0.28 | 0.76       | 0.06      | < 0.001  |
|                           | $\beta^{2*}$ | 0.38  | 1.46       | 0.12      | 0.002    |