Semiparametric estimation of structural failure time model in continuous-time processes

Shu Yang, Karen Pieper, and Frank Cools

Abstract

Structural failure time models are causal models for estimating the effect of time-varying treatments on a survival outcome. G-estimation and artificial censoring have been proposed to estimate the model parameters in the presence of time-dependent confounding and administrative censoring. However, most of existing methods require manually preprocessing data into regularly spaced data, which may invalidate the subsequent causal analysis. Moreover, the computation and inference are challenging due to the non-smoothness of artificial censoring. We propose a class of continuous-time structural failure time models, which respects the continuous time nature of the underlying data processes. Under a martingale condition of no unmeasured confounding, we show that the model parameters are identifiable from potentially infinite estimating equations. Using the semiparametric efficiency theory, we derive the first semiparametric doubly robust estimators, in the sense that the estimators are consistent if either the treatment process model or the failure time model is correctly specified, but not necessarily both. Moreover, we propose using inverse probability of censoring weighting to deal with dependent censoring. In contrast to artificial censoring, our weighting strategy does not introduce non-smoothness in estimation and ensures that the resampling methods can be used to make inference.

Keywords: Causality; Cox proportional hazards model; Discretization; Observational study; Semi-parametric analysis; Survival data.

1 Introduction

Confounding by indication is common in observational studies, which obscures the causal relationship of the treatment and outcome (Robins et al.; 1992). In longitudinal observational studies, this phenomenon becomes more pronounced due to time-varying confounding when there are time-dependent covariates that predict the subsequent treatment and outcome and also are affected by the past treatment history. In this case, standard regression methods whether or not adjusting for confounders are fallible (Robins et al.; 2000; Daniel et al.; 2013).

Structural failure time models (Robins and Tsiatis; 1991; Robins; 1992) and marginal structural models (Robins; 2000; Hernán et al.; 2001) have been used to effectively handle time-varying confounding. Structural failure time models simulate the potential failure time outcome that would have been observed in the absence of treatment by removing the effect of treatment, while marginal structural models specify the marginal relationship of potential outcomes under different treatments possibly adjusting for the baseline covariates. Structural failure time models have certain features that are more desirable than marginal structural models (Robins; 2000): structural failure time models allow for modeling time-varying treatment modification effects using the post baseline time-dependent covariates; they are more flexible to translate biological hypotheses into their parameters (Robins; 1998b; Lok; 2005); and the g-estimation (Robins; 1998b) for structural failure time models does not require the probability of receiving treatment at each time point to be positive for all subjects.
Most of structural failure time models specify deterministic relationships of the observed failure time and the baseline failure time and therefore are rank preserving; see, e.g., Mark and Robins (1993b,a); Robins and Greenland (1994); Robins (2002); Hernán et al. (2003). Moreover, existing g-estimation often uses a discrete-time setup, which requires all subjects to be followed at the same pre-fixed time points. However, in practical situations, the variables and processes are more likely to be measured at irregularly spaced time points, which may not be the same for all subjects (Robins; 1998a). To apply existing estimators, one needs to discretize the timeline and re-create the measurements at each time point e.g. by averaging observations within the given time point or imputation if there are no observations. Such data preprocessing may distort the relationship of variables and cast doubt on the sequential randomization assumption, which however is essential to justify the discrete-time g-estimation (Zhang et al. 2011). In the literature, much less work has been addressing non-rank preserving continuous-time causal models; exceptions include Robins (1998b); Lok et al. (2004); Lok (2008, 2017). Robins (1998b) conjectured that g-estimation extends to the settings with continuous-time processes, which however relies on the rank preserving assumption. Recently, Lok (2017) presented a formal proof for this conjecture without rank preservation.

Despite these advances, estimation for continuous-time structural failure time models is largely underdeveloped. Existing g-estimation is singly robust, in the sense that it relies on a correct model specification for the treatment process. In the literature of missing data analysis and causal inference, many authors have proposed doubly robust estimators that require either one of the two model components to be correctly specified (Robins et al. 1994; Scharfstein et al. 1999; Van Der Laan et al. 2002; Lunceford and Davidian 2004; Bang and Robins 2005; Cao et al. 2009; Robins et al. 2007; Lok and DeGruttola 2012). Yang and Lok (2016) constructed a doubly robust test procedure for structural nested mean models. To our best knowledge, there does not exist a double robust estimator for structural failure time models.

We develop a general framework for structural failure time models with continuous-time processes. We relax the local rank preservation by specifying a distributional instead of deterministic relationship of the treatment process and the potential baseline failure time. We impose a martingale condition of no unmeasured confounding, which serves as the basis for identification and estimation. Under the semiparametric model characterized by the structural failure time model and the no unmeasured confounding assumption, we develop a class of regular asymptotically linear estimators. This class of estimators contains the semiparametric efficient estimators (Bickel et al. 1993; Tsiatis 2006). To ease computation, we further construct an optimal member among a wide class of semiparametric estimators that are relatively simple to compute. Moreover, we show that our estimators are doubly robust, which achieve the consistency if either the model for the treatment process is correctly specified or the failure time model is correctly specified, but not necessarily both. Our framework is readily applicable to the traditional discrete-time settings.

In the presence of censoring, Robins and coauthors have introduced the notion of the potential censoring time and proposed an approach for using this information to estimate the treatment effect. This approach may artificially terminate follow-up for some subjects before their observed failure or censoring times, and therefore it is often called artificial censoring. This approach works only for administrative censoring when follow-up ends at a pre-specified date. It fails to provide consistent estimators for dependent censoring (Rotnitzky and Robins 1995), which likely occurs due to subjects drop out. Moreover, the computation and inference are challenging due to the non-smoothness of artificial censoring (Joffe 2001; Joffe et al. 2012). To overcome these limitations, we propose using inverse probability of censoring weighting to deal with censoring. In contrast to artificial censoring, our weighting strategy is smooth and ensures that the resampling methods can be used for inference, which is straightforward to implement in practice.

2 Notation, models, and assumptions

2.1 Notation

We assume that \( n \) subjects constitute a random sample from a larger population of interest and therefore are independent and identically distributed. For notational simplicity, we suppress the subscript \( i \) for subject. Let \( T \) be the observed failure time. Let \( L_t \) be a multidimensional covariates process, and let \( A_t \) be the
binary treatment process; i.e., \( A_t = 1 \) if the subject is on treatment at time \( t \), and \( A_t = 0 \) if the subject is off treatment at time \( t \). We assume that all subjects received treatment at baseline and may discontinue treatment during follow up. We also assume that treatment discontinuation is permanent; i.e., if \( A_t = 0 \), then \( A_u = 0 \) for all \( u \geq t \). Let \( V \) be the time to treatment discontinuation or failure, whichever came first, and let \( \Gamma \) be the binary indicator of treatment discontinuation at time \( V \). For the purpose of regularity, we assume that all continuous-time processes are càdlàg processes; i.e., the processes are continuous from the right and have limits from the left. Let \( H_t = (L_t, A_t) \) be the combined covariates and treatment process, where we write \( A_t \) for the treatment just before time \( t \). We also use overline to denote the history; e.g., \( \overline{H}_t = (H_u : 0 \leq u \leq t) \) is the history of the covariates and treatment process until time \( t \). Following \cite{Cox1984}, we assume there exists a potential baseline failure time \( U \), representing the failure time outcome had the treatment always been withheld. The full data is \( F = (T, \overline{H}_T) \). We assume that there is no censoring before \( T \) until §4.

### 2.2 Structural failure time model

The structural failure time model specifies the relationship of the potential baseline failure time \( U \) and the actual observed failure time \( T \). We assume that given any \( \overline{H}_t \),

\[
U \sim U(\psi^*) = \int_0^T \exp[\{\psi_1^* + \psi_2^* g(L_u)\}A_u] \, du,
\]

where \( \sim \) means “has the same distribution as”, and \( \psi^* = (\psi_1^*, \psi_2^*) \) is a \( p \)-vector of unknown parameters. Model (1) entails that the treatment effect is to accelerate or decelerate the failure time compared to the baseline failure time \( U \). Intuitively, \( \exp[\{\psi_1^* + \psi_2^* g(L_t)\}A_t] \) can be interpreted as the effect rate of the treatment on the outcome possibly modified by the time-varying covariate \( g(L_t) \). To help understanding the model, consider a simplified model \( U(\psi^*) = \int_0^T \exp(\psi_1^* A_u) \, du \). The multiplicative factor \( \exp(\psi_1^*) \) describes the relative increase/decrease in the failure time had the subject continuously received treatment compared to had the treatment always been withheld.

**Remark 1** The rank-preserving structural failure time model specifies a deterministic relationship instead of a distributional relationship of the failure times; i.e., it uses “\( \sim \)” instead of “\( \simeq \)” in Model (1). Then, for subjects \( i \) and \( j \) who have the same observed treatment and covariate history, \( T_i < T_j \) must imply \( U_i < U_j \). This may be restrictive in practice. In contrast, we link the distribution of the baseline failure time and the distribution of the actual failure time after removing the treatment effect. Specifically, we assume that the distributions of \( U \) and \( U(\psi^*) \) are the same, given past treatment and covariates, which do not impose the rank-preserving restriction.

### 2.3 No unmeasured confounding

The model parameter \( \psi^* \) is not identifiable in general, because \( U \) is missing for all subjects. To identify and estimate \( \psi^* \), we impose the assumption of no unmeasured confounding \cite{Yang2018}.

**Assumption 1 (No Unmeasured Confounding)** The hazard of treatment discontinuation is

\[
\lambda_V(t \mid F, U) = \lim_{h \to 0} h^{-1} P(t \leq V < t + h, \Gamma = 1 \mid F, U, V \geq t) = \lim_{h \to 0} h^{-1} P(t \leq V < t + h, \Gamma = 1 \mid \overline{H}_t, V \geq t) = \lambda_V(t \mid \overline{H}_t).
\]

Assumption 1 implies that \( \lambda_V(t \mid F, U) \) depends only on the past treatment and covariate history until time \( t \), \( \overline{H}_t \), but not on the future variables and \( U \). This assumption holds if the set of historical covariates contains all prognostic factors for the failure time that affect the decision of discontinuing treatment at \( t \).

For an equivalent representation of the treatment process \( A_t \), we define the counting process \( N_V(t) = I(V \leq t, \Gamma = 1) \) and the at-risk process \( Y_V(t) = I(V \geq t) \) \cite{Andersen1993}. Let \( \sigma(H_t) \) be the \( \sigma \)-field
generated by \( H_t \), and let \( \sigma(\overline{H}_t) \) be the \( \sigma \)-field generated by \( \cup_{u \leq t} \sigma(H_u) \). We show in the supplementary material that under Model (1), (2) implies that
\[
\lambda_V \{ t \mid \overline{H}_t, U(\psi^\ast) \} = \lambda_V ( t \mid \overline{H}_t ).
\] (3)
Thus, under common regularity conditions for the counting process, \( M_V ( t ) = N_V ( t ) - \int_t^\infty \lambda_V ( u \mid \overline{H}_u ) Y_V ( u ) d u \) is a martingale with respect to \( \sigma \{ U(\psi^\ast), \overline{H}_t \} \), which renders \( \psi^\ast \) identifiable as we show in § S3. We now focus on semiparametric estimation in the next section.

3 Semiparametric estimation

We consider the semiparametric model characterized by Model (1) and Assumption 1. We derive a regular asymptotically linear estimator \( \hat{\psi} \) of \( \psi^\ast \); i.e.
\[
n^{1/2} ( \hat{\psi} - \psi^\ast ) = P_n \Phi ( F ) + o_p ( 1 ) ,
\] (4)
where \( P_n \) is the empirical measure induced by \( F_1, \ldots, F_n \), i.e., \( P_n \Phi ( F ) = n^{-1} \sum_{i=1}^n \Phi ( F_i ) \), and \( \Phi ( F ) \) is the influence function of \( \hat{\psi} \), which has mean zero and finite and non-singular variance.

Let \( f_T ( T, \overline{P}_T; \psi, \theta ) \) be the semiparametric likelihood function based on a single variable \( F \), where \( \psi \) is the primary parameter of interest, and \( \theta \) is the infinite-dimension nuisance parameter under the semiparametric model. A fundamental result in Bickel et al. (1993) states that the influence functions for regular asymptotically linear estimators lie in the orthogonal complement of the nuisance tangent space, denoted by \( \Lambda^\perp \). We now characterize \( \Lambda^\perp \) and defer the proof to the supplementary material.

**Theorem 1** Under Model (1) and Assumption 1, the orthogonal complement of nuisance tangent space for \( \psi^\ast \) is
\[
\Lambda^\perp = \left\{ \int_0^\infty ( u \{ U(\psi^\ast), \overline{P}_u \} - E [ u \{ U(\psi^\ast), \overline{P}_u \} \mid \overline{P}_u, V \geq u ] ) dM_V ( u ) \right\} , \tag{5}
\]
for all \( p \)-dimensional \( u \{ U(\psi^\ast), \overline{P}_u \} \).

Denote the score function of \( \psi^\ast \) as \( S_\psi ( F ) = \partial \log f_T ( T, \overline{P}_T; \psi, 0 ) / \partial \psi \) evaluated at \( (\psi^\ast, 0) \). Following Bickel et al. (1993), the efficient score for \( \psi^\ast \) is \( S_{\text{eff}} ( F ) = \Pi \{ S_\psi ( F ) \mid \Lambda^\perp \} \), where \( \Pi \) is the projection operator in the Hilbert space. The efficient influence function is \( \Phi ( F ) = E \{ S_{\text{eff}} ( F ) S_{\text{eff}} ( F )^\ast \}^{-1} \), with the variance \( \var [ E \{ S_{\text{eff}} ( F ) S_{\text{eff}} ( F )^\ast \}^{-1} ] \), which achieves the semiparametric efficiency bound. However, the analytical form of \( S_{\text{eff}} ( F ) \) is intractable in general. To facilitate estimation, we focus on a reduced class of \( \Lambda^\perp \) with \( u \{ U(\psi^\ast), \overline{P}_u \} = c(\overline{P}_u) U(\psi^\ast) \) for \( c(\overline{P}_u) \in \mathbb{R}^p \), leading to the estimating function for \( \psi^\ast \):
\[
G(\psi; F ) = \int_0^\infty c(\overline{P}_u) \left\{ U(\psi) - E \left\{ U(\psi) \mid \overline{P}_u, V \geq u \right\} \right\} dM_V ( u ) . \tag{6}
\]
Because of the no unmeasured confounding assumption, \( U(\psi^\ast) \perp M_V ( u ) \mid (\overline{P}_u, V \geq u) \), and therefore \( E \{ G(\psi^\ast; F ) \} = 0 \). We obtain the estimator of \( \psi^\ast \) by solving
\[
P_n \{ G(\psi; F ) \} = 0 . \tag{7}
\]
Within this class, we show that the optimal choice of \( c(\overline{P}_u) \) is
\[
c_{\text{opt}} (\overline{P}_u) = E \left\{ \partial \hat{U}_u ( \psi ) / \partial \psi \mid \overline{P}_u, V = u \right\} \left[ \var [ U(\psi) \mid \overline{P}_u, V \geq u ] \right]^{-1} , \tag{8}
\]
in the sense that with this choice the solution to (7) gives the most precise estimator of \( \psi^\ast \) among all solutions to (7). To use \( c_{\text{opt}} (\overline{P}_u) \), we require positing working models for approximation; see the example in the simulation study. Compared to naive choices, e.g., \( c(\overline{P}_u) = \{ A_u, A_u g(L_u)^T \}^T \) for Model (1), our simulation results show that using the optimal choice gains estimation efficiency.
In [7], we assume that the model for the treatment process and \( E \{ U(\psi) \mid \Pi_u, V \geq u \} \) are known. In practice, they are often unknown and must be modeled and estimated from the data. We posit a proportional hazards model with time-dependent covariates; i.e.,

\[
\lambda_V(t \mid \Pi_t; \gamma_V) = \lambda_{V,0}(t) \exp \{ \gamma_V^T g_V(t, \Pi_t) \},
\]

where \( \lambda_{V,0}(t) \) is unknown and non-negative, \( g_V(t, \Pi_t) \) is a pre-specified function of \( t \) and \( \Pi_t \), and \( \gamma_V \) is a vector of unknown parameters. We also posit a working model \( E \{ U(\psi) \mid \Pi_u, V \geq u; \xi \} \), indexed by \( \xi \). We show that the estimating equation for \( \psi^* \) achieves the double robustness or double protection [Rotnitzky and Vansteelandt, 2015].

**Theorem 2 (Double robustness)** Under Model [7] and Assumption [4] the estimating equation [7] for \( \psi^* \) is unbiased of zero if either the model for the treatment process is correctly specified, or the failure time model \( E \{ U(\psi) \mid \Pi_u, V \geq u; \xi \} \) is correctly specified, but not necessarily both.

4 Censoring

4.1 Inverse probability of censoring weighting

In most studies, the failure time is subject to right censoring. We now introduce \( C \) to be the time to censoring. The observed data are \( O = \{ X = \min(T, C), \Delta = 1(T \leq C), \Pi_X \} \). In the presence of censoring, we may not observe \( T \) and calculate \( U(\psi) \), and consequently the estimating equation [7] is not feasible to solve. A naive solution is to replace \( T \) in \( U(\psi) \) by \( X \) and use \( \tilde{U}(\psi) = \int_0^X \exp(\psi A_u)du \); however, \( \tilde{U}(\psi^*) \) depends on the whole treatment process and therefore is not independent of \( M_V(t) \) given \( \Pi_t \), which renders the estimating equation [7] biased [Hernán et al., 2005]. Robins (1998b) suggested a strategy to deal with administrative censoring. In this case, \( C \) is independent of all other variables. This strategy replaces \( U(\psi) \) by a function of \( U(\psi) \) and \( C \) which is always observable. For illustration, we consider \( U(\psi) = \int_0^T \exp(\psi A_u)du \) and

\[
C(\psi) = \min_{a \in (0,1]} \int_0^C \exp(\psi a_s)ds = \begin{cases} C, & \text{if } \psi \geq 0, \\ C \exp(\psi), & \text{if } \psi < 0. \end{cases}
\]

Then, \( \tilde{U}(\psi^*) = \min \{ U(\psi^*), C(\psi^*) \} \) and \( \Delta(\psi^*) = 1 \{ U(\psi^*) < C(\psi^*) \} \) are the two functions that are independent of \( M_V(t) \) given \( \Pi_t \) and are always computable; see the supplementary material. G-estimator is then constructed based on \( \tilde{U}(\psi) \) and \( \Delta(\psi) \). In this approach, for subjects with \( T < C \), it may be possible that \( U(\psi) > C(\psi) \) and \( \Delta(\psi) = 0 \), which considers these subjects who actually were observed to fail as if they were censored. Therefore, this approach is often called artificial censoring. Artificial censoring suffers from many drawbacks. First, the resulting estimating equation is not smooth in \( \psi \), and therefore estimation and inference are challenging [Joffe et al., 2012]. Second, if the censoring mechanism is dependent, the estimators will be inconsistent [Robins, 1998b]. To avoid the drawbacks of artificial censoring and also allow for more general censoring mechanisms, we consider an alternative approach using inverse probability of censoring weighting. Robins (1998b) suggested and Witteman et al. (1998) applied the weighting approach to deal with censoring by competing risks in the deterministic structural nested failure time models with discretized data.

We assume an ignorable censoring mechanism as follows.

**Assumption 2** The hazard of censoring is

\[
\lambda_C(t \mid F, T > t) = \lim_{h \to 0} h^{-1} P(t \leq C < t + h \mid C \geq t, F, T > t) \\
= \lim_{h \to 0} h^{-1} P(t \leq C < t + h \mid C \geq t, \Pi_t, T > t) = \lambda_C(t \mid \Pi_t, T > t),
\]

denoted by \( \lambda_C(t \mid \Pi_t) \) for shorthand.
Assumption 2 states that $\lambda_C(t \mid F, T > t)$ depends only on the past treatment and covariate history until time $t$, but not on the future variables and failure time. This assumption holds if the set of historical covariates contains all prognostic factors for the failure time that affect the lost to follow up at time $t$. Under this assumption, the missing data due to censoring are missing at random (Rubin, 1976). In the presence of censoring, redefine $V$ as the time to treatment discontinuation or failure or censoring, whichever came first. We show in the supplementary material that $\lambda_V(t \mid \mathcal{P}_t)$ is equal to $\lambda_V(t \mid \mathcal{P}_t, C \geq t)$ and therefore can be estimated conditional on $V \geq t$ with the new definition of $V$. From $\lambda_C(t \mid \mathcal{P}_t)$, we define $K_C(t \mid \mathcal{P}_t) = \exp \left\{ - \int_0^t \lambda_C(u \mid \mathcal{P}_u) \, du \right\},$ which is the probability of the subject not being censored before time $t$. For regularity, we also impose a positivity condition for $K_C(t \mid \mathcal{P}_t)$.

Assumption 3 (Positivity) There exists a constant $\delta$ such that with probability one, $K_C(t \mid \mathcal{P}_t) \geq \delta > 0$ for $t$ in the support of $T$.

Under Assumptions 2, 3, $\psi^*$ is identifiable; see the supplementary material for proof. Following Rotnitzky et al. (2009), the main idea of inverse probability of censoring weighting is to re-distribute the weights for the censored subjects to the remaining “similar” uncensored subjects.

**Theorem 3** Under Assumptions 2, 3, the unbiased estimating equation for $\psi^*$ is

$$P_n \left\{ \frac{\Delta}{K_C(T \mid \mathcal{H}_T)} G(\psi; F) \right\} = 0,$$

where $G(\psi; F)$ is defined in (9).

Theorem 3 assumes that $\lambda_C(t \mid \mathcal{H}_t)$ is known. Similar to $\lambda_V(t \mid \mathcal{P}_t)$, we posit a proportional hazards model with time-dependent covariates:

$$\lambda_C(t \mid \mathcal{P}_t) = \lambda_{C,0}(t) \exp \left\{ \gamma_C^T g_C(t, \mathcal{P}_t) \right\},$$

where $\lambda_{C,0}(t)$ is unknown and non-negative, $g_C(t, \mathcal{P}_t)$ is a pre-specified function of $t$ and $\mathcal{P}_t$, and $\gamma_C$ is a vector of unknown parameters.

To summarize, the algorithm for developing an estimator of $\psi^*$ is as follows.

**Step 1.** Using the data $(V_i, \Gamma_i, \mathcal{P}_{V_i,i}), i = 1, \ldots, n$, fit a model for $\lambda_V(t \mid \mathcal{P}_t) = \lambda_{V,0}(t) \exp \{ \gamma_V^T g_V(t, \mathcal{P}_t) \}$.

To estimate $\gamma_V$, treat the treatment discontinuation as “failure” and the failure event and censoring as “censored” observations in the time-dependent proportional hazards model. Once we have an estimate of $\gamma_V$, $\hat{\gamma}_V$, we can estimate the cumulative baseline hazard, $\lambda_{V,0}(t)dt$ using the Breslow estimator

$$\hat{\lambda}_{V,0}(t)dt = \frac{\sum_{i=1}^n dN_{V_i}(t)}{\sum_{i=1}^n \exp \{ \gamma_V^T g_V(t, \mathcal{P}_{i,i}) \} Y_{V_i}(t)}.$$

Then, obtain $\hat{M}_V(t) = N_V(t) - \int_0^t \exp \{ \gamma_V^T g_V(u, \mathcal{P}_u) \} \hat{\lambda}_{V,0}(u)Y_V(u)du$.

**Step 2.** Using the data $(X_i, \Delta_i, \mathcal{P}_{X_i,i}), i = 1, \ldots, n$, derive the estimator of $\lambda_C(t \mid \mathcal{P}_t) = \lambda_{C,0}(t) \exp \{ \gamma_C^T g_C(t, \mathcal{P}_t) \}$, and obtain the estimator of $K_C(T_i \mid \mathcal{H}_{T_i})$. To estimate $\gamma_C$, treat censoring as “failure” and the failure event as “censored” observations in the time-dependent proportional hazards model. Once we have an estimate of $\gamma_C$, $\hat{\gamma}_C$, we can estimate $\lambda_{C,0}(t)dt$ using the Breslow estimator

$$\hat{\lambda}_{C,0}(t)dt = \frac{\sum_{i=1}^n dN_{C_i}(t)}{\sum_{i=1}^n \exp \{ \gamma_C^T g_C(t, \mathcal{P}_{i,i}) \} Y_{C_i}(t)}$$

where $N_C(t) = I(C \leq t, \Delta = 0)$ and $Y_C(t) = I(C \geq t)$ are the counting process and the at-risk process of observing censoring. Then, we estimate $K_C(t \mid \mathcal{H}_t)$ by

$$K_C(t \mid \mathcal{H}_t) = \prod_{0 \leq u \leq t} \left[ 1 - \exp \{ \gamma_C^T g_C(u, \mathcal{P}_u) \} \hat{\lambda}_{C,0}(u)du \right].$$
Step 3. We obtain the estimator \( \hat{\psi} \) of \( \psi \) by solving

\[
P_n \left\{ \frac{\Delta}{K_C(T | \overline{P}_T)} \int c(\overline{P}_u) \left[ U(\psi) - E \left\{ U(\psi) \mid \overline{P}_u, V \geq u; \xi \right\} \right] dM_V(u) \right\} = 0, \tag{13}\]

where we estimate \( E \left\{ U(\psi) \mid \overline{P}_u, V \geq u; \xi \right\} \) by regressing \( \tilde{K}_C(T \mid \overline{P}_T)^{-1} \Delta U(\psi) \) on \((X_0, L_u, u)\) restricted to subjects with \( V \geq u \). The estimating equation \( \text{(13)} \) is continuously differentiable on \( \psi \) and thus can be generally solved using a Newton-Raphson procedure (Atkinson, 1989). For example, one can use the function “multiroot” in R.

Remark 2 It is worth discussing the connection between the proposed estimator and the existing framework for discrete time points. If the processes take observations at discrete times \( \{t_0, \ldots, t_K\} \), then, for \( t = t_m, \overline{P}_t = \{H_{t_1}, \ldots, H_{t_m}\} \), \( dN_T(t) \) is a binary treatment indicator, and \( \int_0^1 \lambda_T(u \mid \overline{P}_u) Y_T(u) du \) becomes the propensity score \( P\{dN_T(t) = 1 \mid \overline{P}_t\} \). As a result, \( \text{(13)} \) with \( E \left\{ U(\psi) \mid \overline{P}_u, V \geq u; \xi \right\} \) being zero simplifies to the existing estimation equation for \( \psi^* \). Importantly, \( \text{(13)} \), for the first time in the literature, provides the semiparametric doubly robust estimator \( \hat{\psi} \) even for discrete time setting, in that \( \hat{\psi} \) is consistent if either the model for the treatment process or the failure time model is correctly specified, under correct model specifications for the treatment effect mechanism and the censoring.

4.2 Asymptotic theory and variance estimation

In this section we discuss the asymptotic properties of our proposed estimator with technical details presented in the supplementary material. To reflect the dependence of the estimating equation on the nuisance models, denote \( \text{(13)} \) as \( P_n \Phi(\psi; \xi, \tilde{M}_V, \tilde{K}_C; F) = 0 \), where \( \Phi(\psi; \xi, M_V, K_C; F) = \{K_C(T \mid \overline{P}_T)^{-1} \Delta \int c(\overline{P}_u) U(\psi) - E \left\{ U(\psi) \mid \overline{P}_u, V \geq u; \xi \right\} \} dM_V(u) \). Let the probability limits of \( \tilde{\xi}, \tilde{M}_V \), and \( \tilde{K}_C \) be \( \xi^*, M_V^*, \) and \( K_C^* \), respectively. We impose standard regularity conditions for \( Z \)-estimators (van der Vaart and Wellner, 1996) as formulated by Assumptions S1-S4. Roughly speaking, these conditions restrict the flexibility and convergence rates of the nuisance estimators; e.g., we assume that \( \Phi(\psi; \xi, M_V, K_C; F) \) and \( \partial \Phi(\psi; \xi, M_V, K_C; F) / \partial \psi \) belong to \( P \)-Donsker classes, and the regularity conditions ensure that

\[
E \left( \int c(\overline{P}_u) \left[ \left( \frac{U(\psi^*)}{\partial U(\psi^*) / \partial \psi} \right) \mid \overline{P}_u, V \geq u; \tilde{\xi} \right] - E \left( \left( \frac{U(\psi^*)}{\partial U(\psi^*) / \partial \psi} \right) \mid \overline{P}_u, V \geq u; \xi^* \right) \right) d \left\{ \tilde{M}_V(u) - M_V^*(u) \right\} = o_p(n^{-1/2}).
\]

Under Assumptions S3 and S4, Theorem S6 states that if \( K_C \) is correctly specified, and if either \( E \{ U(\psi) \mid \overline{P}_u, V \geq u; \xi \} \) or \( M_V \) is correctly specified, \( \hat{\psi} \) solving \( \text{(11)} \) with the estimated nuisance models is still consistent and asymptotically normal, with the influence function \( \hat{\Phi}(\psi^*, \xi^*, M_V^*, K_C^*; F) \).

We can estimate the variance of \( \hat{\psi} \) either by the empirical variance of the estimated influence function or by resampling. If all nuisance models, \( \xi, M_V, \) and \( K_C \), are correctly specified, we obtain an analytical expression for \( \hat{\Phi}(\psi^*, \xi^*, M_V^*, K_C^*; F) \) as in (S10). We can then estimate \( \hat{\Phi}(\psi^*, \xi^*, M_V^*, K_C^*; F) \) by plugging in estimates of \( \psi^*, \xi^*, M_V^*, K_C^* \), and the required expectations, denoted by \( \tilde{\Phi}(\psi, \xi, M_V, K_C; F) \). Then, the estimated variance of \( n^{1/2}(\hat{\psi} - \psi^*) \) is

\[
P_n \left\{ \hat{\Phi}(\psi; \xi, \tilde{M}_V, \tilde{K}_C; F) \tilde{\Phi}(\psi, \xi, \tilde{M}_V, \tilde{K}_C; F)^T \right\}.
\tag{14}\]

However, when either \( \xi \) or \( M_V \) is correctly specified but not both, characterizing \( \tilde{\Phi}(\psi^*, \xi^*, M_V^*, K_C^*; F) \) is difficult, and therefore approximating \( \text{(14)} \) is no longer feasible. To avoid the technical difficulty, we recommend estimating the asymptotic variance with the resampling methods such as bootstrap and Jackknife (Efron, 1979; Efron and Stein, 1981). In this case, the resampling works because \( \hat{\psi} \) is regular and asymptotically normal.
5 Simulation study

We evaluate the finite sample performance of the proposed estimator on simulated data sets. We generate $U$ from $\text{Exp}(0.2)$ and generate the covariate process $(X_0, L_t)$ had the treatment always been withheld, where $X_0 \sim \text{Bernoulli}(0.55)$. To generate $L_t$, we first generate a $1 \times 3$ row vector following a multivariate normal distribution with mean equal to $(0.2U - 4)$ and covariance equal to $0.7^{j-i}$ for $i,j = 1,2,3$. This vector represents the values of $L_t$ at times $t_1 = 0$, $t_2 = 5$, and $t_3 = 10$. We assume that the time-dependent variable remains constant between measurements. We generate the time until treatment discontinuation, $V_1$, according to a proportional hazards model $\lambda_V(t \mid X_0, L_t) = 0.15 \exp(0.15X_0 + 0.15L_t)$. This generates the treatment process $A_i$; i.e., $A_t = 1$ if $t \leq V_1$ and $A_t = 0$ if $t > V_1$. The observed time-dependent covariate process is $L_t$ if $t \leq V_1$ and $L_t + \log(t - V_1)$ if $t > V_1$ to reflect that the covariate process is affected after treatment discontinuation. Let the history of covariates and treatment until time $t$ be $\overline{x}_t = (X_0, L_t, A_{t-})$. We generate $T$ according to $U \sim \int_0^T \exp(\psi^* A_u)du$ as follows. Let $T_1 = U \exp(-\psi^*)$. If $T_1 < V_1$, $T = T_1$; otherwise $T = U + V_1 - V_1 \exp(\psi^*)$. Under the above data generating mechanism, the potential failure time under $\overline{x}_T$ also follows a Cox marginal structural model with the hazard rate at $u$, $\lambda_0(u) \exp(\psi^* A_u)$ (Young et al. 2010). We generate $C$ according to a proportional hazards model with $\lambda_C(t \mid X_0, L_t, C \geq t) = 0.025 \exp(0.15X_0 + 0.15L_t)$. Let $X = \min(T, C)$. If $T < C$, $\Delta = 1$; otherwise $\Delta = 0$. Finally, let $V = \min(V_1, T, C)$ and $\Gamma$ be the indicator of treatment discontinuation before the time to failure or censoring; i.e., if $V = V_1$, $\Gamma = 1$; otherwise $\Gamma = 0$. The observed data are $(X_i, \Delta_i, V_i, \Gamma_i, \overline{x}_{X_i, i})$ for $i = 1, \ldots, n$. We consider $\psi^* \in \{-0.5, 0, 0.5\}$. From our data generating mechanism, 50% – 58% observations are censored, and 70% – 80% treatment discontinuation times are observed before the time to failure or censoring.

We consider the following estimators of $\psi^*$: (i) an naive estimator $\widehat{\psi}_{\text{naive}}$ by solving (1) with $T$ in $U(\psi) = \int_0^T \exp(\psi^* A_u)du$ replaced by $X$; (ii) an inverse probability of weighting estimator of the Cox marginal structural model $\psi_{\text{msm}}$ (Yang et al. 2013); (iii) a simple inverse probability of censoring weighting estimator $\widehat{\psi}_{\text{ipcw}}$ by solving $P_n [\widehat{K}_C(T \mid \overline{H}_T)^{-1} \Delta \int c(\overline{H}_u) U(\psi) dM_T(u)] = 0$; and (iv) the proposed doubly robust estimator $\widehat{\psi}_{\text{dr}}$ by solving (13) with $E \{U(\psi) \mid \overline{H}_u, V \geq u\}$ reducing to a tractable function $E \{U(\psi) \mid \overline{H}_0\}$. Note that $\psi_{\text{ipcw}}$ is the special case of $\psi_{\text{dr}}$ with $E \{U(\psi) \mid \overline{H}_u, V \geq u\}$ being misspecified as zero. Moreover, to demonstrate the impact of data discretization, we include the discrete-time g-estimator $\widehat{\psi}_{\text{disc}}$ applied to the pre-processed data with the grid size 51. We present the details for $\psi_{\text{msm}}$ and $\psi_{\text{disc}}$ in the supplementary material. For estimators requiring the choice of $c(\overline{H}_u)$, we compare a simple choice $c(\overline{H}_u) = A_{u-}$ and the optimal choice $c^{\text{opt}}(\overline{H}_u)$ in (8), where $\{\partial U_u(\psi) / \partial \psi \mid \overline{H}_u, V = u\} = E(V - u \mid \overline{H}_u, V \geq u)$. We approximate $E(V - u \mid \overline{H}_u, V \geq u)$ by the mean of exponential distribution with the rate $\lambda_V(u)$ and assume that $\text{var} \{U(\psi) \mid \overline{H}_u, V \geq u\}$ is a constant, which is common practice in the generalized estimating equation literature. We approximate $E \{U(\psi) \mid \overline{H}_u, V \geq u\}$ by regressing $\widehat{K}_C(T \mid \overline{H}_T)^{-1} \Delta U(\psi)$ on $(X_0, L_0)$. To evaluate the double robustness, we consider two specifications for the hazard of treatment discontinuation: (a) the true proportional hazards model, and (b) a misspecified Kaplan-Meier model (Kaplan and Meier 1958). In calculating the censoring weights, we specify the censoring model as the true proportional hazards model. We assess the impact of misspecification of the censoring model in the supplementary material. For standard errors, we consider the delete-a-group Jackknife variance estimator with 500 groups (Kott 1998).

Table 1 summarizes the simulation results with $n = 1,000$. The naive estimator $\widehat{\psi}_{\text{naive}}$ is biased, and its bias becomes larger as $|\psi^*|$ increases. In scenario 1 where the treatment process model is correctly specified, $\widehat{\psi}_{\text{ipcw}}$, $\widehat{\psi}_{\text{dr}}$, and $\widehat{\psi}_{\text{msm}}$ show small biases across all scenarios with different values $\psi^*$. Note that $\widehat{\psi}_{\text{ipcw}}$ is a special case of the proposed estimator with $E \{U(\psi) \mid \overline{H}_u, V \geq u\}$ being misspecified as zero. This demonstrates that the proposed estimator is robust to misspecification of $E \{U(\psi) \mid \overline{H}_u, V \geq u\}$ given that the treatment process model is correctly specified. If additionally $E \{U(\psi) \mid \overline{H}_u, V \geq u\}$ is well approximated, $\widehat{\psi}_{\text{dr}}$ gains estimation efficiency over $\widehat{\psi}_{\text{ipcw}}$. Moreover, $\widehat{\psi}_{\text{dr}}$, with $c^{\text{opt}}$ are more efficient than that with $c$. Moreover, in scenario 1, $\widehat{\psi}_{\text{dr}}$ has smaller standard errors than $\widehat{\psi}_{\text{msm}}$. This is because $\widehat{\psi}_{\text{msm}}$ involves weighting directly by the inverse of the propensity score, whereas $\widehat{\psi}_{\text{dr}}$ utilizes the propensity score not in a form of inverse weights and therefore avoids the possibly large variability due to weighting. In scenario 2 where the treatment process model is misspecified, $\widehat{\psi}_{\text{ipcw}}$ and $\widehat{\psi}_{\text{msm}}$ show large biases; however, $\widehat{\psi}_{\text{dr}}$ still has small biases, confirming its
Table 1: Simulation results: bias, standard deviation, root mean squared error, and coverage rate of 95% confidence intervals for $\exp(\psi^*)$ over 1,000 simulated datasets: Scenario 1/2 the treatment discontinuation model is correctly specified/misspecified.

| Scenario | Model | $\psi^* = -0.5$ | Bias | S.E. | C.R. | Bias | S.E. | C.R. | Bias | S.E. | C.R. |
|----------|-------|-----------------|------|------|------|------|------|------|------|------|------|
|          | $\hat{\psi}_{naive}$ | $c$ | 0.06 | 0.048 | 76.8 | 0.02 | 0.069 | 95.6 | -0.06 | 0.112 | 92.4 |
|          | $\hat{\psi}_{opt}$   | $c$ | 0.05 | 0.043 | 78.4 | 0.02 | 0.063 | 95.0 | -0.05 | 0.107 | 91.8 |
|          | $\hat{\psi}_{ipcw}$  | $c$ | -0.01 | 0.089 | 95.2 | -0.02 | 0.123 | 97.2 | -0.02 | 0.191 | 95.6 |
|          | $\hat{\psi}_{dr}$    | $c$ | 0.00 | 0.053 | 95.2 | -0.00 | 0.076 | 96.8 | -0.01 | 0.125 | 95.4 |
|          | $\hat{\psi}_{msm}$   | $c$ | -0.00 | 0.050 | 95.8 | 0.00 | 0.081 | 96.4 | 0.00 | 0.148 | 95.2 |
|          | $\hat{\psi}_{disc}$  | $c$ | -0.37 | 0.041 | 0.0 | -0.61 | 0.055 | 0.0 | -1.01 | 0.092 | 0.6 |
|          | $\hat{\psi}_{naive}$ | $c$ | 0.22 | 0.065 | 4.8 | 0.24 | 0.097 | 30.4 | 0.26 | 0.164 | 66.0 |
|          | $\hat{\psi}_{ipcw}$  | $c$ | 0.16 | 0.098 | 62.4 | 0.23 | 0.140 | 64.4 | 0.33 | 0.239 | 79.6 |
|          | $\hat{\psi}_{dr}$    | $c$ | 0.01 | 0.048 | 95.0 | 0.00 | 0.070 | 96.4 | 0.00 | 0.115 | 95.4 |
|          | $\hat{\psi}_{msm}$   | $c$ | 0.13 | 0.069 | 54.4 | -0.40 | 0.051 | 57.6 | 0.36 | 0.217 | 75.6 |
|          | $\hat{\psi}_{disc}$  | $c$ | -0.25 | 0.035 | 0.0 | 0.22 | 0.118 | 0.0 | -0.72 | 0.092 | 1.0 |

6 Application to the GARFIELD data

We present an analysis for the Global Anticoagulant Registry in the FIELD with Atrial Fibrillation (GARFIELD-AF) registry study, an observational study of patients with newly diagnosed atrial fibrillation. See the study website at [http://www.garfieldregistry.org](http://www.garfieldregistry.org) for details. Our analysis includes 22,811 patients, who were enrolled between April 2013 and August 2016 and received oral anticoagulant therapy for stroke prevention. Our goal is to investigate the effect of discontinuation of oral anticoagulant therapy in patients with atrial fibrillation. The primary end point is the composite clinical outcome including death, non-haemorrhagic stroke, systemic embolism, and myocardial infarction. We define a patient as permanently discontinuing if treatment was stopped for at least 7 days and never re-started afterwards. In our study, 9.5% of patients discontinued oral anticoagulant therapy over a median follow-up of 710 days with an interquartile range (487, 731) days; 43.8% of discontinuations were within the first 4 months of the start of treatment. Among those who discontinued treatment, 512 patients stopped the treatment for more than 7 days and went back on treatment. This is called switching. We censor the switches at the time of restarting treatment. This censoring mechanism is not likely to be completely at random, because patients with poor prognosis may be more likely to switch. We assume a dependent censoring mechanism and use inverse probability of censoring weighting.

To answer the clinical question of interest, we consider the structural failure time model $U(\psi^*) = \int_0^T \exp(\psi^* A_u) du$. Under this model, if a patient had been on treatment continuously, $T = U(\psi^*) \exp(-\psi^*)$, so $U(\psi^*) \{\exp(-\psi^*) - 1\}$ is the time gained/reduced while on treatment. We focus on estimating the mul-
Table 2: Results of the effect of oral anticoagulant therapy on the composite outcome: $\exp(\psi^*)$ is the causal estimand

|                | Est | S.E. | C.I.     | p-value |
|----------------|-----|------|----------|---------|
| Naive method   | 0.68| 0.176| (0.34, 1.03) | 0.07    |
| Proposed method| 0.64| 0.179| (0.29, 0.99)  | 0.04    |

multiplicative factor $\exp(\psi^*)$. Table 2 reports the results from the naive estimator and the proposed doubly robust estimator as described in §5. We describe the details for the nuisance models in the supplementary material. Although the effect sizes may be a little different between the naive analysis and the proposed analysis, qualitatively they all suggest that treatment is beneficial for prolonging the time to clinical events, and therefore treatment discontinuation is harmful. If a patient had been on treatment continuously versus if the patient had never taken treatment, the time to clinical outcomes would have been $\exp(-\hat{\psi}) = 1/0.64 = 1.56$ times longer. Importantly, the proposed analysis is designed to address the well-formulated question for investigating the effect of treatment discontinuation.

7 Discussion

The proposed framework of structural failure time model can be used to adjust for time-varying confounding and selection bias with irregularly spaced observations under three assumptions of no unmeasured confounders, ignorability of censoring, and positivity. As discussed previously, Assumptions 1 and 2 hold if all variables that are related to both treatment discontinuation and outcome and that are related to both censoring and outcome are measured. Although essential, they are not verifiable based on the observed data but rely on subject matter experts to assess their plausibility. The future work will investigate the sensitivity to these assumptions using the methods in Yang and Lok (2017). Assumption 3 states that all subjects have nonzero probabilities of staying on study before the failure time. This assumption requires the absence of predictors that are deterministic in relation to censoring and outcome. Practitioners should carefully examine the question at hand to eliminate deterministic violations of positivity.

Our framework can also be extended in the following directions. First, the proposed doubly robust estimator with respect to model specifications for the treatment process and the baseline failure time; however, it still relies on a correct specification of the censoring mechanism. If the censoring model is misspecified, the proposed estimator may be biased; see the additional simulation results in the supplementary material. It would be interesting to construct an improved estimator that is multiply robust in the sense that such an estimator is consistent in the union of the three models (Molina et al. 2017). Second, it is critical to derive test procedures for evaluating the goodness-of-fit of the treatment effect model. The key insight is that we have more unbiased estimating equations than the model parameters. In future work, we will derive tests based on over-identification restrictions tests (Yang and Lok 2016) for evaluating a treatment effect model.

Acknowledgment

We benefited from the comments from two reviewers and Anastasio A. Tsiatis. Dr. Yang is partially supported by ORAU, NSF DMS 1811245, and NCI P01 CA142538.

Supplementary Material

Supplementary material available at Biometrika online includes proofs, technical details and additional simulation. R package is available at https://github.com/shuyang1987/contTimeCausal.
References

Andersen, P. K., Borgan, O., Gill, R. D. and Keiding, N. (1993). *Statistical Models based on Counting Processes*, Springer-Verlag, New York.

Atkinson, K. E. (1989). *An Introduction to Numerical Analysis*, Wiley, New York.

Bang, H. and Robins, J. M. (2005). Doubly robust estimation in missing data and causal inference models, *Biometrics* 61: 962–973.

Bickel, P. J., Klaassen, C., Ritov, Y. and Wellner, J. (1993). *Efficient and Adaptive Inference in Semiparametric Models*, Johns Hopkins University Press, Baltimore.

Cao, W., Tsiatis, A. A. and Davidian, M. (2009). Improving efficiency and robustness of the doubly robust estimator for a population mean with incomplete data, *Biometrika* 96: 723–734.

Cox, D. R. and Oakes, D. (1984). *Analysis of Survival Data*, London: Chapman and Hall.

Daniel, R., Cousens, S., De Stavola, B., Kenward, M. and Sterne, J. (2013). Methods for dealing with time-dependent confounding, *Stat Med* 32: 1584–1618.

Efron, B. (1979). Bootstrap methods: Another look at the jackknife, *Ann. Statist.* 7: 1–26.

Efron, B. and Stein, C. (1981). The jackknife estimate of variance, *Ann. Statist.* 9: 586–596.

Hernán, M. Á., Brumback, B. and Robins, J. M. (2000). Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men, *Epidemiology* 11: 561–570.

Hernán, M. A., Cole, S. R., Margolick, J., Cohen, M. and Robins, J. M. (2005). Structural accelerated failure time models for survival analysis in studies with time-varying treatments, *Pharmacoepidemiology and Drug Safety* 14: 477–491.

Joffe, M. M. (2001). Administrative and artificial censoring in censored regression models, *Stat Med* 20(15): 2287–2304.

Joffe, M. M., Yang, W. P. and Feldman, H. (2012). G-estimation and artificial censoring: Problems, challenges, and applications, *Biometrics* 68: 275–286.

Kaplan, E. L. and Meier, P. (1958). Nonparametric estimation from incomplete observations, *J Am Stat Assoc* 53: 457–481.

Kott, P. S. (1998). Using the delete-a-group jackknife variance estimator in practice, *Survey Res. Meth. Sect.*, *Am. Statist. Assoc.* pp. 763–768.

Lok, J., Gill, R., Van Der Vaart, A. and Robins, J. (2004). Estimating the causal effect of a time-varying treatment on time-to-event using structural nested failure time models, *Statistica Neerlandica* 58: 271–295.

Lok, J. J. (2008). Statistical modeling of causal effects in continuous time, *Ann. Statist.* 36: 1464–1507.

Lok, J. J. (2017). Mimicking counterfactual outcomes to estimate causal effects, *Ann. Statist.* 45: 461–499.

Lok, J. J. and DeGruttola, V. (2012). Impact of time to start treatment following infection with application to initiating haart in HIV-positive patients, *Biometrics* 68: 745–754.

Lunceford, J. K. and Davidian, M. (2004). Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study, *Stat Med* 23: 2937–2960.
Mark, S. D. and Robins, J. M. (1993a). Estimating the causal effect of smoking cessation in the presence of confounding factors using a rank preserving structural failure time model, *Stat Med* **12**: 1605–1628.

Mark, S. D. and Robins, J. M. (1993b). A method for the analysis of randomized trials with compliance information: an application to the multiple risk factor intervention trial, *Control Clin Trials* **14**: 79–97.

Molina, J., Rotnitzky, A., Sued, M. and Robins, J. (2017). Multiple robustness in factorized likelihood models, *Biometrika* **104**: 561–581.

Robins, J. (1992). Estimation of the time-dependent accelerated failure time model in the presence of confounding factors, *Biometrika* **79**(2): 321–334.

Robins, J. M. (1998a). Correction for non-compliance in equivalence trials, *Stat Med* **17**: 269–302.

Robins, J. M. (1998b). Structural nested failure time models, in C. T. Armitage P (ed.), *The Encyclopedia of Biostatistics*, Wiley, Chichester, UK: Wiley, pp. 4372–4389.

Robins, J. M. (2000). Marginal structural models versus structural nested models as tools for causal inference, *Statistical Models in Epidemiology, the Environment, and Clinical Trials*, Springer, New York, pp. 95–133.

Robins, J. M. (2002). Analytic methods for estimating HIV-treatment and cofactor effects, *Methodological Issues in AIDS Behavioral Research*, Springer, New York, pp. 213–288.

Robins, J. M., Blevins, D., Ritter, G. and Wulfsohn, M. (1992). G-estimation of the effect of prophylaxis therapy for pneumocystis carinii pneumonia on the survival of AIDS patients, *Epidemiology* **3**: 319–336.

Robins, J. M. and Greenland, S. (1994). Adjusting for differential rates of prophylaxis therapy for PCP in high-versus low-dose AZT treatment arms in an AIDS randomized trial, *J Am Stat Assoc* **89**: 737–749.

Robins, J. M., Hernan, M. A. and Brumback, B. (2000). Marginal structural models and causal inference in epidemiology, *Epidemiology* **11**: 550–560.

Robins, J. M., Rotnitzky, A. and Zhao, L. P. (1994). Estimation of regression coefficients when some regressors are not always observed, *J Am Stat Assoc* **89**: 846–866.

Robins, J. M. and Tsiatis, A. A. (1991). Correcting for non-compliance in randomized trials using rank preserving structural failure time models, *Comm. Statist. Theory* **20**: 2609–2631.

Robins, J., Sued, M., Lei-Gomez, Q. and Rotnitzky, A. (2007). Comment: Performance of double-robust estimators when "inverse probability" weights are highly variable, *Statist. Sci.* **22**: 544–559.

Rotnitzky, A., Bergesio, A. and Farall, A. (2009). Analysis of quality-of-life adjusted failure time data in the presence of competing, possibly informative, censoring mechanisms, *Lifetime Data Anal* **15**(1): 1–23.

Rotnitzky, A. and Robins, J. M. (1995). Semiparametric regression estimation in the presence of dependent censoring, *Biometrika* **82**: 805–820.

Rotnitzky, A. and Vansteelandt, S. (2015). Double-robust methods, in A. Tsiatis and G. Verbeke (eds), *Handbook of Missing Data Methodology*, Boca Raton, FL: CRC Press., pp. 185–212.

Rubin, D. B. (1976). Inference and missing data, *Biometrika* **63**: 581–592.

Scharfstein, D. O., Rotnitzky, A. and Robins, J. M. (1999). Adjusting for nonignorable drop-out using semiparametric nonresponse models, *J Am Stat Assoc* **94**: 1096–1120.

Tsiatis, A. (2006). *Semiparametric Theory and Missing Data*, Springer, New York.
Van Der Laan, M. J., Hubbard, A. E. and Robins, J. M. (2002). Locally efficient estimation of a multivariate survival function in longitudinal studies, *J Am Stat Assoc* **97**: 494–507.

den Vaart, A. W. and Wellner, J. A. (1996). *Weak Convergence and Empirical Processes: With Applications to Statistics*, New York: Springer.

Witteman, J. C., D'Agostino, R. B., Stijnen, T., Kannel, W. B., Cobb, J. C., de Ridder, M. A., Hofman, A. and Robins, J. M. (1998). G-estimation of causal effects: isolated systolic hypertension and cardiovascular death in the Framingham Heart Study, *Am J Epidemiol* **148**: 390–401.

Yang, S. and Lok, J. J. (2016). A goodness-of-fit test for structural nested mean models, *Biometrika* **103**: 734–741.

Yang, S. and Lok, J. J. (2017). Sensitivity analysis for unmeasured confounding in coarse structural nested mean models, *Statist. Sinica* **28**: 1703–1723.

Yang, S., Tsiatis, A. A. and Blazing, M. (2018). Modeling survival distribution as a function of time to treatment discontinuation: A dynamic treatment regime approach, *Biometrics* **74**: 900–909.

Young, J. G., Hernán, M. A., Picciotto, S. and Robins, J. M. (2010). Relation between three classes of structural models for the effect of a time-varying exposure on survival, *Lifetime Data Analysis* **16**: 71–84.

Zhang, M., Joffe, M. M. and Small, D. S. (2011). Causal inference for continuous-time processes when covariates are observed only at discrete times, *Ann. Statist.* **39**: 131–173.
Supplementary Material

S1 A lemma

We provide a lemma for the martingale process, which is useful in our derivation later.

Consider the Hilbert space $\mathcal{H}$ of all $p$-dimensional, mean-zero finite variance measurable functions of $F, h(F)$, equipped with the covariance inner product $\langle h_1, h_2 \rangle = E \{ h_1(F)^T h_2(F) \}$ and the norm $||h|| = [E \{ h(F)^T h(F) \}]^{1/2} < \infty$.

**Lemma S1** Under Assumption 1, $M_V(t)$ is a martingale with respect to the filtration $\sigma\{\overline{T}, U(\psi^*)\}$. By Proposition II.4.1 in [Andersen et al., 1993], $M_V(t)$ has a unique compensator $< M_V(t) = \int_0^t \lambda_V(u \mid \overline{T}_u)Y_V(u)du$. If $g_1(\cdot)$ and $g_2(\cdot)$ are bounded $\sigma\{\overline{T}, U(\psi^*)\}$-predictable processes, then

$$< \int_0^t g_1(u)dM_V(u), \int_0^t g_2(u)dM_V(u) >$$

exists, and

$$< \int_0^t g_1(u)dM_V(u), \int_0^t g_2(u)dM_V(u) > = \int_0^t g_1(u)g_2(u)\lambda_V(u \mid \overline{T}_u)Y_V(u)du. \quad (S1)$$

S2 Proof of (3)

To show (3), it suffices to show that $\lambda_V\{ t \mid \overline{T}_t, U(\psi^*) \} = \lambda_V(t \mid \overline{T}_t, U).$ We obtain

$$\lambda_V(t \mid \overline{T}_t, U) = \lim_{h \to 0} h^{-1} P( t \leq V < t + h, \Gamma = 1 \mid V \geq t, \overline{T}_t, U)$$

$$= \lim_{h \to 0} h^{-1} \frac{P( t \leq V < t + h, \Gamma = 1, \overline{T}_t ) P(t \leq V < t + h, \Gamma = 1 \mid V \geq t, \overline{T}_t)}{P( V \geq t, \Gamma = 1, \overline{T}_t )}$$

$$= \lim_{h \to 0} h^{-1} \frac{P\{ U(\psi^*) \mid t \leq V < t + h, \Gamma = 1, \overline{T}_t \} P(t \leq V < t + h, \Gamma = 1 \mid V \geq t, \overline{T}_t)}{P\{ U(\psi^*) \mid V \geq t, \Gamma = 1, \overline{T}_t, U(\psi^*) \}}$$

$$= \lambda_V\{ t \mid \overline{T}_t, U(\psi^*) \},$$

where the second equality follows by the Bayes rule, and the third equality follows by Model 1 which entails that the distributions of $(U, \overline{T}_t)$ and $(U(\psi^*), \overline{T}_t)$ are the same.

S3 Identification of $\psi \in \mathbb{R}^p$ under Assumption 1

Under Assumption 1, $M_V(t) = N_V(t) - \int_0^t \lambda_V(u \mid \overline{T}_u)Y_V(u)du$ is a martingale with respect to the filtration $\sigma\{\overline{T}_t, U(\psi^*)\}$. Then, for any $c(\overline{T}_t) \in \mathbb{R}^p$ and $t > 0$,

$$E \left\{ c(\overline{T}_t)U(\psi^*)dM_V(t) \right\} = 0. \quad (S2)$$

Suppose that (S2) holds for $\psi^1$ and $\psi^2$; i.e., for any $c(\overline{T}_t) \in \mathbb{R}^p$ and $t > 0$, $E[c(\overline{T}_t)\{ U(\psi^1) - U(\psi^2) \}dM_V(t)] = 0$. To reflect the dependence of $U(\psi^1) - U(\psi^2)$ on $(\overline{A}_T, \overline{L}_T)$, denote $\varphi(\overline{A}_T, \overline{L}_T) = U(\psi^1) - U(\psi^2) = \int_0^T \exp\{\psi_0^1 + \psi_0^1 \tau g(L_u)\}A_u^1du - \int_0^T \exp\{\psi_0^2 + \psi_0^2 \tau g(L_u)\}A_u^2du$. Then, for any $c(\overline{T}_t) \in \mathbb{R}^p$ and $t > 0$, we have $E \left\{ c(\overline{T}_t)\varphi(\overline{A}_T, \overline{L}_T) \right\}dM_V(t) = 0$. This implies that $\varphi(\overline{A}_T, \overline{L}_T)$ is independent of $M_V(t)$ conditional on $(\overline{T}_t, V > t)$ for all $\overline{T}_t$ and $t > 0$. Therefore, $\varphi(\overline{A}_T, \overline{L}_T)$ must not depend on $\overline{A}_T$, and therefore $\psi^1$ must equal $\psi^2$. Consequently, $\psi^*$ is uniquely identified from (S2).
S4 Proof of Theorem 1

To motivate the concept of the nuisance tangent space for a semiparametric model, we first consider a parametric model \( f(F; \psi, \theta) \), where \( \psi \) is a \( p \)-dimensional parameter of interest, and \( \theta \) is an \( q \)-dimensional nuisance parameter. The score vectors of \( \psi \) and \( \theta \) are \( S_\psi(F) = \partial \log f(F; \psi, \theta^*) / \partial \psi \) and \( S_\theta(F) = \partial \log f(F; \psi^*, \theta) / \partial \theta \), respectively, both evaluated at the true value \((\psi^*, \theta^*)\). For this parametric model, the nuisance tangent space \( \Lambda \) is the linear space in \( \mathcal{H} \) spanned by the nuisance score vector \( S_\theta(F) \). In a semiparametric model, the nuisance parameter \( \theta \) may be infinite-dimensional. The nuisance tangent space \( \Lambda \) is defined as the mean squared closure of the nuisance tangent spaces under any parametric submodel. An important fact is that the orthogonal complement of the nuisance tangent space \( \Lambda^\perp \) contains the influence functions for regular asymptotically linear estimators of \( \psi \).

First, we characterize the semiparametric likelihood function based on a single observable \( F \). Because the transformation of \( F \) to \( \{U(\psi^*), \overline{H}_T\} \) is one-to-one, the likelihood function based on \( F \) becomes

\[
f_F (T, \overline{H}_T) = \left\{ \frac{\partial U(\psi^*)}{\partial T} \right\} f_{\{U(\psi^*), \overline{H}_T\}} \{U(\psi^*), \overline{H}_T\},
\]

where \( \partial U(\psi^*) / \partial T = \exp [A_T(\psi^* + \psi^* g(L_T))] \). Let \( v_0 = 0 < v_1 < \cdots < v_M \) be the observed times to treatment discontinuation among the \( n \) subjects. We further express (S3) as

\[
f_F (T, \overline{H}_T; \psi^*, \theta) = \left\{ \frac{\partial U(\psi^*)}{\partial T} \right\} f_{\{U(\psi^*); \theta_1\}} \prod_{k=1}^{M} f \{L_{v_k} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k; \theta_2\}
\]

\[
\times \prod_{r=v_1}^{v_M} f \{A_{v_k} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k; \theta_3\}
\]

\[
= \left\{ \frac{\partial U(\psi^*)}{\partial T} \right\} f_{\{U(\psi^*); \theta_1\}} \prod_{k=1}^{M} f \{L_{v_k} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k; \theta_2\}
\]

\[
\times \prod_{r=v_1}^{v_M} f \{A_{v_k} | \overline{H}_{v_{k-1}}, T > v_k; \theta_3\},
\]

where the second equality follows from Assumption 1 and 3, \( f_{\{U(\psi^*); \theta_1\}} \), \( f \{L_{v_k} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k\} \), and \( f \{A_{v_k} | \overline{H}_{v_{k-1}}, T > v_k\} \) are completely unspecified, and \( \theta = (\theta_1, \theta_2, \theta_3) \) is a vector of infinite-dimensional nuisance parameters.

Let \( \Lambda_k \) be the nuisance tangent space for \( \theta_k \), for \( k = 1, 2, 3 \). We now characterize \( \Lambda_k \).

For the nuisance parameter \( \theta_1 \), \( f_{\{U(\psi^*); \theta_1\}} \) is a nonparametric model indexed by \( \theta_1 \), i.e., \( f \{U(\psi^*); \theta_1\} \) is a non-negative function and satisfies \( \int f(v; \theta_1) dv = 1 \). Following Section 4.4 of Tsatis (2006), the tangent space regarding \( \theta_1 \) is the set of all vector \( s \{U(\psi^*)\} \in \mathbb{R}^p \) with \( E[s \{U(\psi^*)\}] = 0 \). Thus, the tangent space of \( \theta_1 \) is

\[
\Lambda_1 = \{ s \{U(\psi^*)\} \in \mathbb{R}^p : E[s \{U(\psi^*)\}] = 0 \}.
\]

For the nuisance parameter \( \theta_2 \), \( \prod_{k=1}^{M} f \{L_{v_k} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k; \theta_2\} \) is a nonparametric model indexed by \( \theta_2 \). To obtain the nuisance tangent space of \( \theta_2 \), following the same derivation as for \( \theta_1 \), the score function of \( \theta_2 \) is of the form \( \sum_{k=1}^{M} S \{L_{v_k}, \overline{H}_{v_{k-1}}(\psi^*)\} \), where \( E[S \{L_{v_k}, \overline{H}_{v_{k-1}}(\psi^*)\} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k] = 0 \). Thus, the tangent space of \( \theta_2 \) is

\[
\Lambda_2 = \sum_{k=1}^{M} \{ S \{L_{v_k}, \overline{H}_{v_{k-1}}(\psi^*)\} \in \mathbb{R}^p : E[S \{L_{v_k}, \overline{H}_{v_{k-1}}(\psi^*)\} | \overline{H}_{v_{k-1}}(\psi^*), T > v_k] = 0 \}.
\]

For the nuisance parameter \( \theta_3 \), \( \prod_{k=1}^{M} f \{A_{v_k} | \overline{H}_{v_{k-1}}, T > v_k; \theta_3\} \) can be equivalently expressed as
the likelihood based on the data $(V, \Gamma, \overline{H}_V)$ and the hazard function $\lambda_V(t \mid \overline{H}_t)$:

$$f_{(V, \Gamma, \overline{H}_V)}(V, \Gamma, \overline{H}_V) = \lambda_V(V \mid \overline{H}_V)^{\Gamma} \exp \left\{ - \int_0^V \lambda_V(u \mid \overline{H}_u) du \right\} \times \left\{ f_{T\mid\overline{H}_T}(V \mid \overline{H}_V) \right\}^{1-\Gamma} \left\{ \int_V^{\infty} f_{T\mid\overline{H}_T}(u \mid \overline{H}_u) du \right\}^{\Gamma}.$$ 

Following [Tsatis 2006], the tangent space of $\theta_3$ is

$$\Lambda_3 = \left\{ \int h_u(\overline{\Pi}_u)dM_V(u) : h_u(\overline{\Pi}_u) \in \mathbb{R}^p \right\}.$$ 

Moreover, it is easy to show that $\Lambda_1$, $\Lambda_2$ and $\Lambda_3$ are mutually orthogonal subspaces. Then, $\Lambda = \Lambda_1 \oplus \Lambda_2 \oplus \Lambda_3$, where $\oplus$ denotes a direct sum.

Now, let

$$\Lambda_3^* = \left\{ \int h_u\{U(\psi^\ast), \overline{\Pi}_u\}dM_V(u) : h_u\{U(\psi^\ast), \overline{\Pi}_u\} \in \mathbb{R}^p \right\}.$$ 

Because the tangent space $\Lambda_1 \oplus \Lambda_2 \oplus \Lambda_3^*$ is that for a nonparametric model; i.e., a model that allows for all densities of $F$, and because the tangent space for a nonparametric model is the entire Hilbert space, we obtain $\mathcal{H} = \Lambda_1 \oplus \Lambda_2 \oplus \Lambda_3^*$. Because $\Lambda = \Lambda_1 \oplus \Lambda_2 \oplus \Lambda_3$, this implies that $\Lambda_3 \subset \Lambda_3^*$. Also, the orthogonal complement $\Lambda^\bot$ must be orthogonal to $\Lambda_1 \oplus \Lambda_2$, so $\Lambda^\bot$ must belong to $\Lambda_3^*$ and be orthogonal to $\Lambda_3$. This means that $\Lambda^\bot$ consists of all elements of $\Lambda_3^*$ that are orthogonal to $\Lambda_3$.

To characterize $\Lambda^\bot$, for any $\int h_u\{U(\psi^\ast), \overline{\Pi}_u\}dM_V(u) \in \Lambda_3^*$, we obtain its projection onto $\Lambda_3^\bot$. To find the projection, we derive $h_u^\ast(\overline{\Pi}_u)$ so that

$$\left[ \int h_u\{U(\psi^\ast), \overline{\Pi}_u\}dM_V(u) - \int h_u^\ast(\overline{\Pi}_u)dM_V(u) \right] \in \Lambda_3^\bot.$$ 

Therefore, we have

$$E\left( \int \left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\} - h_u^\ast(\overline{\Pi}_u) \right] dM_V(u) \right) = 0,$$

(S5)

for any $h_u(\overline{\Pi}_u)$. By Lemma $\text{S1}$ ($\text{S3}$) becomes

$$E\left( \int \left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\} - h_u^\ast(\overline{\Pi}_u) \right] h_u(\overline{\Pi}_u)\lambda_V(u \mid \overline{\Pi}_u)Y_V(u) du \right) = 0$$

for any $h_u(\overline{\Pi}_u)$. Because $h_u(\overline{\Pi}_u)$ is arbitrary, we must have

$$E\left( \left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\} - h_u^\ast(\overline{\Pi}_u) \right] Y_V(u \mid \overline{\Pi}_u) h_u(\overline{\Pi}_u) \lambda_V(u \mid \overline{\Pi}_u) du \right) = 0$$

(S6)

Solving (S6) for $h_u^\ast(\overline{\Pi}_u)$, we obtain

$$E\left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\}Y_V(u \mid \overline{\Pi}_u) \right] = h_u^\ast(\overline{\Pi}_u)E\left\{ Y_V(u \mid \overline{\Pi}_u) \right\},$$

or

$$h_u^\ast(\overline{\Pi}_u) = \frac{E\left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\}Y_V(u \mid \overline{\Pi}_u) \right]}{E\left\{ Y_V(u \mid \overline{\Pi}_u) \right\}} = E\left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\} \mid \overline{\Pi}_u, V \geq u \right].$$

Therefore, the space orthogonal to the nuisance tangent space is given by

$$\Lambda^\bot = \left\{ \left( h_u\{U(\psi^\ast), \overline{\Pi}_u\} - E\left[ h_u\{U(\psi^\ast), \overline{\Pi}_u\} \mid \overline{\Pi}_u, V \geq u \right] \right) dM_V(u) : h_u\{U(\psi^\ast), \overline{\Pi}_u\} \in \mathbb{R}^p \right\}.$$
S5 The optimal form $c^{\text{opt}}(\overline{H}_u)$

We obtain the optimal form of $c(\overline{H}_u)$ by projecting the score function $S_\psi(F)$ onto 

$$
\Lambda_0^+ = \left\{ G(\psi^*; F, c) = \int_0^\infty c(\overline{H}_u) \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \text{d}M_V(u) : c(\overline{H}_u) \in \mathbb{R}^p \right\}.
$$

We first characterize the projection of any $B(F) \in \mathcal{H}$ onto $\Lambda_0^+$. For ease of notation, we may suppress the dependence of $F$ of random variables if there is no ambiguity.

**Theorem S4 (Projection)** For any $B = B(F) \in \mathcal{H}$, the projection of $B$ onto $\Lambda_0^+$ is 

$$
\prod \left( B \mid \Lambda_0^+ \right) = \int \left[ E \left\{ BU_u(\psi^*) \mid \overline{H}_u, V = u \right\} - E \left\{ BU_u(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \times \left[ \text{var} \left\{ U(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right]^{-1} \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \text{d}M_V(u),
$$

where $\dot{U}_u(\psi) = U(\psi) - E\{U(\psi) \mid \overline{H}_u, V \geq u\}$.

**Proof.** Let $G(F)$ be the quantity in the right hand side of (S7). To show that $\prod \left( B \mid \Lambda_0^+ \right) = G(F)$, we must show that $B - G \in \Lambda_0$. Toward that end, we show that for any $\dot{G}(F) \in \Lambda_0^+, (B - G) \perp \dot{G}$. Specifically, we need to show that for any $\dot{G}(F) = \int_0^\infty \dot{c}(\overline{H}_u) \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \text{d}M_V(u)$, $E \left\{ (B - G) \dot{G} \right\} = 0$. We now verify that $E \left( B \dot{G} \right) = E \left( G \dot{G} \right)$ by the following calculation.

Firstly, we obtain 

$$
E \left( G \dot{G} \right) = E \left( \langle G, \dot{G} \rangle \right)
$$

$$
= E \int \dot{c}(\overline{H}_u) \left[ E \left\{ BU_u(\psi^*) \mid \overline{H}_u, V = u \right\} - E \left\{ BU_u(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \times \left[ \text{var} \left\{ U(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right]^{-1} \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \text{d}M_V(u),
$$

Secondly, we obtain 

$$
E \left( B \dot{G} \right) = E \int \dot{c}(\overline{H}_u) B \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \overline{H}_u, T \geq u \right\} \right] \text{d}M_V(u)
$$

$$
= E \int \dot{c}(\overline{H}_u) B\dot{U}_u(\psi^*) \text{d}N_V(u) - E \int_0^\infty \dot{c}(\overline{H}_u) B\dot{U}_u(\psi^*) \lambda_V(u \mid \overline{H}_u) Y_V(u) \text{d}u
$$

$$
= E \int \dot{c}(\overline{H}_u) \left[ E \left\{ B\dot{U}_u(\psi^*) \mid \overline{H}_u, V = u \right\} - E \left\{ B\dot{U}_u(\psi^*) \mid \overline{H}_u, V \geq u \right\} \right] \lambda_V(u \mid \overline{H}_u) Y_V(u) \text{d}u,
$$

where the last equality follows because 

$$
E \int \dot{c}(\overline{H}_u) B\dot{U}_u(\psi^*) \text{d}N_V(u) = E \int \dot{c}(\overline{H}_u) E \left\{ B\dot{U}_u(\psi^*) \mid \overline{H}_u, V \geq u \right\} \text{d}N_V(u)
$$

$$
= E \int \dot{c}(\overline{H}_u) E \left\{ B\dot{U}_u(\psi^*) I(u \leq V \leq u + du, \Gamma = 1) \mid \overline{H}_u, V \geq u \right\} \text{d}u
$$

$$
= E \int \dot{c}(\overline{H}_u) E \left\{ B\dot{U}_u(\psi^*) \mid \overline{H}_u, V = u \right\} \lambda_V(u \mid \overline{H}_u) Y_V(u) \text{d}u,
$$

and 

$$
E \int \dot{c}(\overline{H}_u) B\dot{U}_u(\psi^*) \lambda_V(u \mid \overline{H}_u) Y_V(u) \text{d}u = E \int \dot{c}(\overline{H}_u) E \left\{ B\dot{U}_u(\psi^*) \mid \overline{H}_u, V \geq u \right\} \lambda_V(u \mid \overline{H}_u) Y_V(u) \text{d}u.
$$

Therefore, by (S8) and (S9), $E \left( B \dot{G} \right) = E \left( G \dot{G} \right)$ for any $\dot{G} \in \Lambda_0^+$, proving (S7).


Theorem S5 The optimal form of \( \tilde{c}(\tilde{H}_u) \) is (8) in the sense that with this form the solution to (7) gives the most precise estimator of \( \psi^* \) among all the solutions to (7).

Proof. We write \( G(\psi^*; F, c) \) to emphasize its dependence on \( c(\tilde{H}_u) \). We derive the optimal form of \( c(\tilde{H}_u) \) by deriving the most efficient \( G(\psi^*; F, c) \) in \( \Lambda_0^* \), which is \( G(\psi^*; F, c^{opt}) = \prod \left( S^* \mid \Lambda_0^* \right) \).

By Theorem S4 we have

\[
G(\psi^*; F, c^{opt}) = \int \left[ E \left\{ S_0 \tilde{U}_u(\psi^*) \mid \tilde{H}_u, V = u \right\} - E \left\{ S_0 \tilde{U}_u(\psi^*) \mid \tilde{H}_u, V \geq u \right\} \right] \times \left\{ \var{U(\psi^*) \mid \tilde{H}_u, V \geq u} \right\}^{-1} \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \tilde{H}_u, V \geq u \right\} \right] \, dM_V(u). \tag{10}
\]

Because \( E\{\tilde{U}_u(\psi) \mid \tilde{H}_u, V \geq u\} = 0 \), taking the derivative of \( \psi \) at both sides and using the generalized information equality, we have

\[
E\{\tilde{U}_u(\psi) \mid \tilde{H}_u, V \geq u\} = \frac{\partial E\{U(\psi) \mid \tilde{H}_u, V \geq u\}}{\partial \psi}. \tag{11}
\]

Continuing (10),

\[
G(\psi^*; F, c^{opt}) = -\int_0^\infty \left[ E \left\{ \partial \tilde{U}_u(\psi^*) / \partial \psi \mid \tilde{H}_u, V = u \right\} - E \left\{ \partial \tilde{U}_u(\psi^*) / \partial \psi \mid \tilde{H}_u, V \geq u \right\} \right] \times \left\{ \var{U(\psi^*) \mid \tilde{H}_u, V \geq u} \right\}^{-1} \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \tilde{H}_u, V \geq u \right\} \right] \, dM_V(u)
\]

Therefore, by (11), ignoring the negative sign, \( c^{opt}(\tilde{H}_u) \) is given by (8).

S6 Proof of Theorem 2

We show that \( E\{G(\psi^*; F, c) \} = 0 \) in two cases.

First, if \( \lambda_V(t \mid \tilde{H}_t) \) is correctly specified, under Assumption \( M_V(t) \) is a martingale with respect to the filtration \( \sigma(\tilde{H}_u, U(\psi^*)) \). Because \( c(\tilde{H}_u) \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \tilde{H}_u, V \geq u \right\} \right] \) is a \( \sigma(\tilde{H}_t, U(\psi^*)) \)-predictable process, \( \int_0^t c(\tilde{H}_u) \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \tilde{H}_u, V \geq u \right\} \right] \, dM_V(u) \) is a martingale for \( t \geq 0 \). Therefore, \( E\{G(\psi^*; F, c) \} = 0 \).

Second, if \( E\{U(\psi^*) \mid \tilde{H}_u, V \geq u\} \) is correctly specified but \( \lambda_V(t \mid \tilde{H}_t) \) is not necessarily correctly specified, let \( \lambda_V^*(t \mid \tilde{H}_t) \) be the probability limit of the possibly misspecified model. We obtain

\[
E \int c(\tilde{H}_u) \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \tilde{H}_u, V \geq u; \xi^* \right\} \right] \, dN_V(u) - \lambda_V^*(u \mid \tilde{H}_u) Y_V(u) \, du = 0 + E \int c(\tilde{H}_u) E \left( \left[ U(\psi^*) - E \left\{ U(\psi^*) \mid \tilde{H}_u, V \geq u; \xi^* \right\} \right] \mid \tilde{H}_u, V \geq u \right) \times \left\{ \lambda_V(u \mid \tilde{H}_u) - \lambda_V^*(u \mid \tilde{H}_u) \right\} \, Y_V(u) \, du
\]

Therefore, the solution to (7) gives the optimal estimator.
S7 Proof that $\tilde{U}(\psi^*)$ and $\Delta(\psi^*)$ are computable

If $T \leq C$, because $U(\psi^*)$ and $C(\psi^*)$ are observable, $\tilde{U}(\psi^*)$ and $\Delta(\psi^*)$ are computable. If $C < T$, $U(\psi^*)$ is not computable; however, in this case, we shall show that $C(\psi^*) < U(\psi^*)$ corresponding to $\tilde{U}(\psi^*) = C(\psi^*)$ and $\Delta(\psi^*) = 0$, which are computable. Toward this end, by definition of $C(\psi^*)$, we show that when $C < T$, it is always the case that $C(\psi^*) \leq U(\psi^*)$. If $\psi^* \geq 0$, $C(\psi^*) = C \leq T \leq \int_0^T \exp(\psi^* A_u)du = U(\psi^*)$. If $\psi^* < 0$, $C(\psi^*) = C \exp(\psi^*) \leq T \exp(\psi^*) = \int_0^T \exp(\psi^* A_u)du = U(\psi^*)$. This completes the proof.

S8 Proof of $\lambda_V(t \mid \overline{H}_t) = \lambda_V(t \mid \overline{H}_t, C \geq t)$

First, by Assumption 1, we obtain

\[ P(C \geq t \mid t \leq V < t + h, \Gamma = 1, \overline{H}_t) = \exp \left\{ \int_0^t -\lambda_C(u \mid t \leq V < t + h, \Gamma = 1, \overline{H}_t) du \right\} \]

\[ = \exp \left\{ \int_0^t -\lambda_C(u \mid \overline{H}_t) du \right\}, \]

and similarly, we obtain

\[ P(C \geq t \mid V \geq t, \Gamma = 1, \overline{H}_t) = \exp \left\{ \int_0^t -\lambda_C(u \mid V \geq t, \Gamma = 1, \overline{H}_t) du \right\} \]

\[ = \exp \left\{ \int_0^t -\lambda_C(u \mid \overline{H}_t) du \right\}. \]

Consequently, $P(C \geq t \mid t \leq V < t + h, \Gamma = 1, \overline{H}_t) = P(C \geq t \mid V \geq t, \Gamma = 1, \overline{H}_t)$.

Now, by the Bayes rule, we express

\[ \lambda_V(t \mid \overline{H}_t, C \geq t) = \lim_{h \to 0} h^{-1} P(t \leq V < t + h, \Gamma = 1 \mid V \geq t, \overline{H}_t, C \geq t) \]

\[ = \lim_{h \to 0} h^{-1} \frac{P(t \leq V < t + h, \Gamma = 1 | V \geq t, \overline{H}_t) P(C \geq t | t \leq V < t + h, \Gamma = 1, \overline{H}_t)}{P(C \geq t | V \geq t, \overline{H}_t)} \]

\[ = \lim_{h \to 0} h^{-1} P(t \leq V < t + h, \Gamma = 1 | V \geq t, \overline{H}_t) = \lambda_V(t \mid \overline{H}_t). \]

S9 Identification of $\psi \in \mathbb{R}^p$ under Assumptions 1–3

Under Assumptions 2 and 3 for any $c(\overline{H}_t) \in \mathbb{R}^p$ and $t > 0$,

\[ E \left\{ \frac{\Delta}{K_C(T \mid \overline{H}_T)} c(\overline{H}_t) U(\psi^*) dM_V(t) \right\} = E \left\{ c(\overline{H}_t) U(\psi^*) dM_V(t) \right\} = 0. \]  \hspace{1cm} (S14)

Because under Assumption 1, $\psi^*$ is uniquely identified from (S2). Therefore, under Assumptions 1, 3, $\psi^*$ is uniquely identified from (S14).

S10 Proof of Theorem 3

To show (11) is an unbiased estimating equation, it suffices to show that

\[ E \left\{ \frac{\Delta}{K_C(T \mid \overline{H}_T)} G(\psi^*; F) \right\} = 0. \]
Toward that end, by the iterative expectation, we have
\[
E \left\{ \frac{\Delta}{K_C(T \mid H_T)} G(\psi^*; F) \right\} = E \left[ E \left\{ \frac{\Delta}{K_C(T \mid H_T)} G(\psi^*; F) \mid F \right\} \right]
\]
\[
= E \left\{ \frac{E(\Delta \mid F)}{K_C(T \mid H_T)} G(\psi^*; F) \right\}
\]
\[
= E \{ 1 \times G(\psi^*; F) \} = 0,
\]
where the third equality follows by the dependent censoring mechanism specified in (10).

**S11 The asymptotic properties of the proposed estimator**

To establish the asymptotic properties of the proposed estimator, we first introduce additional notation.

Recall the nuisance models (i) \(E\{U(\psi^*) \mid \overline{T}_u, V \geq u; \xi\}\) indexed by \(\xi\); (ii) the proportional hazards model for the treatment process [9], indexed by \(M_\nu\); and (iii) the proportional hazards model for the censoring process [12], indexed by \(K_C\). \(\xi, \tilde{M}_\nu\), and \(\tilde{K}_C\) are the estimates of \(\xi, M_\nu\), and \(K_C\) under the specified parametric and semiparametric models. The probability limits of \(\xi, \tilde{M}_\nu\), and \(\tilde{K}_C\) are \(\xi^*, M_\nu^*,\) and \(K_C^*\). If the failure time model is correctly specified, \(E\{U(\psi^*) \mid \overline{T}_u, V \geq u; \xi^*\} = E\{U(\psi^*) \mid \overline{T}_u, V \geq u\}\); if the model for the treatment process is correctly specified, \(M_\nu^* = M_\nu\); and if the model for the censoring process is correctly specified, \(K_C^* = K_C\).

To reflect that the estimating function depends on the nuisance parameters, we define
\[
\Phi(\psi, \xi, M_\nu, K_C; F) = \frac{\Delta G(\psi, \xi, M_\nu; F)}{K_C(T \mid H_T)},
\]
\[
G(\psi, \xi, M_\nu; F) = \int c(\overline{T}_u) [U(\psi) - E\{U(\psi) \mid \overline{T}_u, V \geq u; \xi\}] dM_\nu(t).
\]

Let \(P\) denote the true data generating distribution, and for any \(f(F)\), let \(P\{f(F)\} = \int f(x) dP(x)\). We define
\[
J_1(\xi) = P\{ \Phi(\psi^*, \xi, M_\nu^*, K_C^*; F) \},
\]
\[
J_2(M^\nu) = P\{ \Phi(\psi^*, \xi^*, M_\nu, K_C^*; F) \},
\]
\[
J_3(K_C) = P\{ \Phi(\psi^*, \xi^*, M_\nu^*, K_C; F) \},
\]
and
\[
J(\xi, M_\nu, K_C) = P\{ \Phi(\psi^*, \xi, M_\nu, K_C; F) \}.
\]

We now assume the regularity conditions, which are standard in the empirical process literature [van der Vaart and Wellner, 1996]. See also [Yang and Lok, 2016] for the application of the empirical process to derive a goodness-of-fit test for the structural nested mean models.

**Assumption S1** With probability going to one, \(\Phi(\psi, \xi, M_\nu, K_C; F)\) and \(\partial \Phi(\psi, \xi, M_\nu, K_C; F) / \partial \psi\) are \(P\)-Donsker classes.

**Assumption S2** For \((\xi^*, M_\nu^*, K_C^*)\) with either \(\xi^*\) being the true parameter such that \(E\{U(\psi^*) \mid \overline{T}_u, V \geq u; \xi^*\} = E\{U(\psi^*) \mid \overline{T}_u, V \geq u\}\) or \(M_\nu^* = M_\nu\) and \(K_C^* = K_C\),
\[
P \left\{ \| \Phi(\psi^*, \tilde{\xi}, \tilde{M}_\nu, \tilde{K}_C; F) - \Phi(\psi^*, \xi^*, M_\nu^*, K_C^*; F) \| \right\} \to 0
\]
and
\[
P \left\{ \| \frac{\partial}{\partial \psi^*} \Phi(\tilde{\psi}, \tilde{\xi}, \tilde{M}_\nu, \tilde{K}_C; F) - \frac{\partial}{\partial \psi} \Phi(\psi^*, \xi^*, M_\nu^*, K_C^*; F) \| \right\} \to 0
\]
in probability.
Assumption S3 \( A(\psi^*, \xi^*, M_V^*, K_C^*) = P \{ \partial \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F)/\partial \psi \} \) is invertible.

Assumption S4 Assume that
\[
\begin{align*}
J(\hat{\xi}, \hat{M}_V, \hat{K}_C) - J(\xi^*, M_V^*, K_C^*) &= J_1(\hat{\xi}) - J_1(\xi^*) + J_2(\hat{M}_V) - J_2(M_V^*) \\
&\quad + J_3(\hat{K}_C) - J_3(K_C^*) + o_p(n^{-1/2}),
\end{align*}
\]
and that \( J_1(\hat{\xi}), J_2(\hat{M}_V), \) and \( J_3(\hat{K}_C) \) are regular asymptotically linear with influence function \( \Phi_1(\psi^*, \xi^*, M_V^*, K_C^*; F), \Phi_2(\psi^*, \xi^*, M_V^*, K_C^*; F), \) and \( \Phi_3(\psi^*, \xi^*, M_V^*, K_C^*; F), \) respectively.

Assumption S1 is an empirical process condition. This assumption is technical and depends on the submodel chosen models for the unknown parameters. Assuming the positivity condition for the censoring process, this assumption can typically be considered as a regularity condition.

Assumption S2 basically states that \( \hat{\xi}, \hat{M}_V, \) and \( \hat{K}_C \) are consistent for \( \xi^*, M_V^*, \) and \( K_C \) and requires that
\[
E \left\{ \int c(\Pi_u) \left[ E \left\{ U(\psi) \mid \Pi_u, V \geq u; \hat{\xi} \right\} - E \left\{ U(\psi) \mid \Pi_u, V \geq u; \xi^* \right\} \right] \right\} \left\{ \hat{\lambda}_V(u) - \lambda_V^*(u) \right\} du = o_p(n^{-1/2}),
\]
and
\[
E \left\{ \int c(\Pi_u) \left[ E \left\{ \frac{\partial U(\psi)}{\partial \psi} \mid \Pi_u, V \geq u; \hat{\xi} \right\} - E \left\{ \frac{\partial U(\psi)}{\partial \psi} \mid \Pi_u, V \geq u; \xi^* \right\} \right] \right\} \left\{ \hat{\lambda}_V(u) - \lambda_V^*(u) \right\} du = o_p(n^{-1/2}).
\]

Because smooth functionals of parametric or semiparametric maximum likelihood estimators for a given model are efficient under regularity conditions, Assumption S3 holds under regularity conditions if \( \hat{\xi} \) and \( \hat{M}_V \) are the parametric and semiparametric maximum likelihood estimators of \( \xi^* \) and \( M_V^* \) under the specified models.

We present the asymptotic properties of the proposed estimator \( \hat{\psi} \) solving equation \( (\Pi) \), denoted by
\[
P_n \left\{ \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) \right\} = 0.
\]

Theorem S6 Under Assumptions S3 and S4, \( n^{1/2} \left( \hat{\psi} - \psi^* \right) \) is consistent and asymptotically linear with the influence function \( \tilde{\Phi}(\psi^*, \xi^*, M_V^*, K_C^*; F) = A(\psi^*, \xi^*, M_V^*, K_C^*)^{-1} \tilde{B}(\psi^*, \xi^*, M_V^*, K_C^*; F), \) and
\[
\tilde{B}(\psi^*, \xi^*, M_V^*, K_C^*; F) = \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_1(\psi^*, \xi^*, M_V^*, K_C^*; F) \\
+ \Phi_2(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_3(\psi^*, \xi^*, M_V^*, K_C^*; F). \tag{S15}
\]
Moreover, if the nuisance models including the models for the censoring process and the treatment process and the outcome model are correctly specified, \( (S15) \) becomes
\[
\tilde{B}(\psi^*, \xi^*, M_V, K_C; F) = \Phi(\psi^*, \xi^*, M_V, K_C; F) - \prod \left\{ \Phi(\psi^*, \xi^*, M_V, K_C; F) \mid \hat{\lambda} \right\}
\]
\[
= \Phi(\psi^*, \xi^*, M_V, K_C; F) - E \left\{ \Phi(\psi^*, \xi^*, M_V, K_C; F)S_{\gamma V}^T \right\} E \left( S_{\gamma V}S_{\gamma V}^T \right)^{-1} S_{\gamma V} \\
- E \left\{ \Phi(\psi^*, \xi^*, M_V, K_C; F)S_{\gamma C}^T \right\} E \left( S_{\gamma C}S_{\gamma C}^T \right)^{-1} S_{\gamma C} \\
+ \int \frac{E \left[ G(\psi^*, \xi^*, K_V; F) \exp \left\{ \gamma_{C}g_c(u, \Pi_u) \right\} \Delta/K_C(T \mid \Pi_T) \right] dM_C(u)}{E \left[ \exp \left\{ \gamma_{C}g_c(u, \Pi_u) \right\} Y_C(u) \right]} \\
+ \int \frac{E \left[ G(\psi^*, \xi^*, K_V; F) \exp \left\{ \gamma_{V}g_v(u, \Pi_u) \right\} \Delta/K_C(T \mid \Pi_T) \right] dM_V(u)}{E \left[ \exp \left\{ \gamma_{V}g_v(u, \Pi_u) \right\} Y_V(u) \right]} \tag{S16}
\]

8
Proof S1} We assume that the model for the censoring process is correctly specified, either the outcome model or the model for the treatment process is correctly specified.

Taylor expansion of \( P_n \left\{ \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) \right\} = 0 \) around \( \psi^* \) leads to

\[
0 = P_n \left\{ \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) \right\} = P_n \left\{ \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) \right\} + P_n \left\{ \frac{\partial \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F)}{\partial \psi^*} \right\} (\hat{\psi} - \psi^*),
\]

where \( \hat{\psi} \) is on the line segment between \( \hat{\psi} \) and \( \psi^* \).

Under Assumptions S1 and S2

\[
(P_n - P) \left\{ \frac{\partial \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F)}{\partial \psi^*} \right\} = (P_n - P) \left\{ \frac{\partial \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F)}{\partial \psi^*} \right\} = o_p(n^{-1/2}),
\]

and therefore,

\[
P_n \left\{ \frac{\partial \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F)}{\partial \psi^*} \right\} = P \left\{ \frac{\partial \Phi(\hat{\psi}, \hat{\xi}, \hat{M}_V, \hat{K}_C; F)}{\partial \psi^*} \right\} + o_p(n^{-1/2}) = A(\psi^*, \xi^*, M_V^*, K_C^*) + o_p(n^{-1/2}).
\]

We then have

\[
n^{1/2}(\hat{\psi} - \psi^*) = A(\psi^*, \xi^*, M_V^*, K_C^*)^{-1} n^{1/2} P_n \left\{ \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) \right\} + o_p(1). \tag{S17}
\]

To evaluate \( \text{S17} \) further,

\[
P_n \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) = (P_n - P) \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F)
\]
\[
+ P \left\{ \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) - \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) \right\} + P \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F). \tag{S18}
\]

Based on the double robustness, the third term becomes

\[
P \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) = 0. \tag{S19}
\]

By Assumptions S1 and S2, the first term becomes

\[
(P_n - P) \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) = (P_n - P) \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) + o_p(n^{-1/2}) = P_n \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) + o_p(n^{-1/2}). \tag{S20}
\]

By Assumption S4 the second term becomes

\[
P \left\{ \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) - \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) \right\} = J(\hat{\xi}, \hat{M}_V, \hat{K}_C) - J(\xi^*, M_V^*, K_C^*) + o_p(n^{-1/2}) = J(\hat{\xi}) - J(\xi^*) + J(M_V) - J(M_V^*) + J(\hat{K}_C) - J(K_C^*) + o_p(n^{-1/2}) = P_n \left\{ \Phi_1(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_2(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_3(\psi^*, \xi^*, M_V^*, K_C^*; F) \right\}. \tag{S21}
\]

Combining S20, S19 with S18,

\[
P_n \Phi(\psi^*, \hat{\xi}, \hat{M}_V, \hat{K}_C; F) = P_n \left\{ \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) \right\},
\]

where

\[
\tilde{B}(\psi^*, \xi^*, M_V^*, K_C^*; F) = \Phi(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_1(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_2(\psi^*, \xi^*, M_V^*, K_C^*; F) + \Phi_3(\psi^*, \xi^*, M_V^*, K_C^*; F).
\]
Therefore, \( \hat{\psi} - \psi^* \) has the influence function

\[
\Phi(\psi^*, \xi^*, M_V, K_C; F) = \{ A(\psi^*, \xi^*, M_V, K_C) \}^{-1} \Phi(\psi^*, \xi^*, M_V, K_C; F).
\]

As a result,

\[
n^{1/2}(\hat{\psi} - \psi^*) = n^{1/2} P_n \Phi(\psi^*, \xi^*, K_V, K_C; F) + o_p(1). \tag{S22}
\]

Based on (S22),

\[
n^{1/2}(\hat{\psi} - \psi^*) \to N(0, \Omega),
\]
as \( n \to \infty \), where \( \Omega = E \{ \Phi(\psi^*, \xi^*, M_V, K_C; F) \Phi(\psi^*, \xi^*, M_V, K_C; F)^T \} \).

For the special case where both nuisance models are correctly specified, we characterize \( \Phi(\psi^*, \xi^*, K_V, K_C; F) \). In this case, \( E \{ \bar{U}(\psi^*) \mid \bar{T}_u, V \geq u; \xi^* \} = E \{ U(\psi^*) \mid \bar{T}_u, V \geq u \} \), \( M_V = M_V \), and \( K_C = K_C \). Define the score functions: \( S_\gamma = S_\gamma \{ U(\psi^*), \bar{T}_u, V \geq u \}, \)

\[
S_\gamma = \int \left\{ \frac{g_V(u, \bar{T}_u) - E \left[ \frac{g_V(u, \bar{T}_u) \exp \left\{ \gamma^T g_V(u, \bar{T}_u) \right\} Y_V(u) \right]} {E \left[ \exp \left\{ \gamma^T g_V(u, \bar{T}_u) \right\} Y_V(u) \right]} \right\} dM_V(u),
\]

and

\[
S_{\gamma C} = \int \left\{ \frac{g_C(u, \bar{T}_u) - E \left[ \frac{g_C(u, \bar{T}_u) \exp \left\{ \gamma^T g_C(u, \bar{T}_u) \right\} Y_C(u) \right]} {E \left[ \exp \left\{ \gamma^T g_C(u, \bar{T}_u) \right\} Y_C(u) \right]} \right\} dM_C(u).
\]

The tangent space for \( \xi \) is \( \tilde{\Lambda}_1 = \{ S_{\xi} \in \mathbb{R}^p : E(\xi) \mid \bar{T}_u, V \geq u = 0 \} \). Following Tsiatis (2006), the nuisance tangent space for the proportional hazards model (1) is

\[
\tilde{\Lambda}_2 = \left\{ S_{\gamma V} + \int h(u) dM_V(u) : h(u) \in \mathbb{R}^p \right\},
\]

and the nuisance tangent space for the proportional hazards model (12) is

\[
\tilde{\Lambda}_3 = \left\{ S_{\gamma C} + \int h(u) dM_C(u) : h(u) \in \mathbb{R}^p \right\}.
\]

Assuming that the treatment process and the censoring process can not jump at the same time point, \( \tilde{\Lambda}_1 \), \( \tilde{\Lambda}_2 \), and \( \tilde{\Lambda}_3 \) are mutually orthogonal to each other. Therefore, the nuisance tangent space for \( \xi \) and the proportional hazards models (1) and (12) is \( \tilde{\Lambda} = \tilde{\Lambda}_1 \oplus \tilde{\Lambda}_2 \oplus \tilde{\Lambda}_3 \). The influence function for \( \hat{\psi} \) is

\[
\Phi(\psi^*, \xi^*, M_V, K_C; F) = \Phi(\psi^*, \xi^*, M_V, K_C; F) - \prod \{ \Phi(\psi^*, \xi^*, M_V, K_C; F) \mid \tilde{\Lambda} \}
\]

\[
= \Phi(\psi^*, \xi^*, M_V, K_C; F) - E \{ \Phi(\psi^*, \xi^*, M_V, K_C; F) S_{\gamma V}^T \} E \left( S_{\gamma V} S_{\gamma V}^T \right)^{-1} S_{\gamma V}
\]

\[
- E \{ \Phi(\psi^*, \xi^*, M_V, K_C; F) S_{\gamma C}^T \} E \left( S_{\gamma C} S_{\gamma C}^T \right)^{-1} S_{\gamma C}
\]

\[
+ \int \frac{E \left[ G(\psi^*, \xi^*, M_V; F) \exp \left\{ \gamma^T g_C(u, \bar{T}_u) \right\} \Delta / K_C(T \mid \bar{T}_u) \right]} {E \left[ \exp \left\{ \gamma^T g_C(u, \bar{T}_u) \right\} Y_C(u) \right]} dM_C(u)
\]

\[
+ \int \frac{E \left[ G(\psi^*, \xi^*, M_V; F) \exp \left\{ \gamma^T g_V(u, \bar{T}_u) \right\} \Delta / K_C(T \mid \bar{T}_u) \right]} {E \left[ \exp \left\{ \gamma^T g_V(u, \bar{T}_u) \right\} Y_V(u) \right]} dM_V(u).
\]

**S12 The Cox marginal structural model approach: \( \hat{\psi}_{\text{msm}} \)**

The Cox marginal structural model approach assumes that the potential failure time under \( \bar{T}_F \) follows a Cox proportional hazards model with the hazard rate at \( t \) as \( \lambda_0(t) \exp(\psi^* a_t) \).
If all potential failure times were observed for all subjects, one can fit a Cox proportional hazards model with the time-varying covariate $a_t$ to obtain a consistent estimator of $\psi^*$. However, not all potential outcomes are observed for a particular subject. To obtain a consistent estimator based on the actual observed data, the key step is to construct time-dependent inverse probability of treatment weights for all subjects and weight their contributions so that they mimic the contributions had all potential outcomes been observed.

From the hazard of treatment discontinuation $\lambda_V(t | \overline{Y}_t)$ defined in (2), denote

$$K_V(t | \overline{Y}_t) = \exp\left\{-\int_0^t \lambda_V(u | \overline{Y}_u) du\right\}$$  \hspace{1cm} (S23)

and

$$f_V(t | \overline{Y}_t) = \lambda_V(t | \overline{Y}_t) K_V(t | \overline{Y}_t).$$  \hspace{1cm} (S24)

For ease of notation, denote $K_V(t) = K_V(t | \overline{Y}_t)$ and $f_V(t) = f_V(t | \overline{Y}_t)$ for shorthand. These can be viewed as the probability of not having discontinued before time $t$ and the probability of discontinuing at time $[t, t + dt)$, respectively.

Consider subjects who were at risk at time $t$. We consider two subsets of individuals: group (a) with $V \leq t$ and $\Gamma = 1$ and group (b) with $V > t$. Specifically, we construct the time-dependent inverse probability of treatment weight as

$$\omega(t) = \begin{cases} \theta(V)/f_V(V), & \text{if } V \leq t \text{ and } \Gamma = 1, \\ \overline{\theta}(t)/K_V(t) & \text{if } V > t, \end{cases}$$ \hspace{1cm} (S25)

where $\theta(t)$ and $\overline{\theta}(t) = \int_t^\infty \theta(u) du$ serve as the stabilized weights [Hernán et al., 2000]. Following Yang et al., 2013, one can consider $\theta(t) = \lambda_{V,0}(t) \exp\left\{-\int_0^t \lambda_{V,0}(u) du\right\}$. In the presence of censoring, let $\omega(t)$ be a product of (S25) and the inverse of censoring probability $\Delta/K_C(T | \overline{Y}_T)$. One can estimate the weights by replacing the unknown quantities with their estimates following Steps 1 and 2 in § 4.1.

Finally, we obtain $\hat{\psi}_{\text{msm}}$ by fitting a Cox proportional hazards model with the time-varying covariate $A_t$ with the time-dependent weight $\omega(t)$ using the standard software; e.g., the function “coxph” in R with the weighting argument.

**S13** The discrete-time g-estimator: $\hat{\psi}^{\text{disc}}$

The existing framework for fitting the structural failure time model is using a discrete time points setting which requires manually discretizing the data. We discretize the timeline into equally-spaced time points from 0 to the maximum follow up $\tau$, denoted as $0 = t_0 < t_1 < \cdots < t_K = \tau$. For $m \geq 1$, at the $m$th time point $t_m$, let $A_{t_m}$ be the indicator of whether the treatment is received at $t_m$, let $L_{t_m}$ be the average of $L_t$ from $t_m-1 \leq t \leq t_m$, let $H_{t_m}$ be the vector of $A_{t_m-1}$ and $L_{t_m}$, and finally let $\overline{Y}_{t_m}$ be $\{H_0, \ldots, H_{t_m}\}$. With observations at discrete time points, $dN_T(t_m)$ becomes the binary treatment indicator $A_{t_m}$, $\lambda_T(u | \overline{Y}_u)Y_T(u) du$ becomes the propensity score $E(A_{t_m} | \overline{Y}_{t_m}, \overline{A}_{t_m-1} = \overline{0})$, and the integral in (7) becomes the summation from $m = 1$ to $K$. As a result, in the absence of censoring, (7) simplifies to the existing estimating equation for structural nested failure time models [Hernán et al., 2005]. Following Hernán et al., 2005, one can estimate the propensity score by the pooled logistic regression model with baseline and time-dependent covariates. In the presence of censoring, one can estimate the censoring probability by the pooled logistic regression model with baseline and time-dependent. The g-estimator $\hat{\psi}^{\text{disc}}$ of $\psi^*$ solves the estimating equation (13) with observations at discrete time points.

**S14** Details and additional results in the simulation

In this section, we present details for the Jackknife method for variance estimation and additional simulation results to assess the impact of misspecification of the censoring model and the treatment effect model.
Table S3: Simulation results: bias, standard deviation, root mean squared error, and coverage rate of 95% confidence intervals for $\exp(\psi^*)$ over 1,000 simulated datasets: Setting 1 where the censoring model is misspecified, and Setting 2 where the treatment effect model is misspecified

| Setting 1 | Setting 2 |
|-----------|-----------|
| $\psi^* = -0.5$ | $\psi^* = 0$ | $\psi^* = 0.5$ |
| $\hat{\psi}_{\text{naive}}$ | 0.06 | 0.05 | -0.02 |
| | 0.07 | 0.08 | 0.02 |
| $\hat{\psi}_{\text{ipcw}}$ | 0.14 | 0.13 | -0.02 |
| | 0.08 | 0.07 | 0.02 |
| $\hat{\psi}_{\text{dr}}$ | 0.04 | 0.04 | -0.02 |
| | 0.08 | 0.07 | 0.02 |
| $\hat{\psi}_{\text{msm}}$ | -0.40 | -0.41 | -0.38 |
| $\hat{\psi}_{\text{disc}}$ | -0.65 | -0.63 | -0.63 |

The Jackknife method entails dividing the subjects into exclusive and exhaustive subgroups, creating replicate datasets by deleting one group at a time, and applying the same estimation procedure to obtain the replicates of $\hat{\psi}$. The variance estimator is $\hat{V}(\hat{\psi}) = G^{-1}(G - 1) \sum_{k=1}^{G} (\hat{\psi}^{(k)} - \bar{\psi})^2$, where $G$ is the number of subgroups, and $\hat{\psi}^{(k)}$ is the $k$th replicate of $\hat{\psi}$.

We now focus on the scenario 1 of the simulation study in §5. First in setting 1, to illustrate the impact of misspecification of the censoring model, for all estimators, we consider an incorrect independent censoring mechanism for fitting the censoring model in the sense that the censoring indicator is independent of all other variables. Second in setting 2, to illustrate the impact of misspecification of the treatment effect model, we now generate the failure time, $T$, according to a structural failure time model $U \sim \int_0^T \exp(\psi^* A_u + 0.5X_0)du$. All estimators are the same as in §5.

Table S3 summarizes the simulation results with $n = 1,000$. In setting 1 when the censoring model is misspecified, the proposed estimators have larger biases compared to the results when the censoring model is correctly specified as in Table 1. In setting 2 when the treatment effect model is misspecified, the proposed estimators also have increased biases compared to the results when the treatment effect model is correctly specified as in Table 1. The coverage rates are off the nominal coverage in most of cases.

### S15 Nuisance models in the application

In this section, we provide details for fitting the nuisance models in the application. To build a model for $\lambda_V(t \mid \mathcal{I}_t)$ in (2), we consider the baseline covariates $X$, including age, gender, race, site, country, and other 25 baseline health outcome measures. For each categorical variable, we create dummy variables. This leads to 99 baseline variables. We first fit a Cox proportional hazards model for $\lambda_V(t \mid \mathcal{I}_t)$ to the data including...
the baseline variables with a $l_1$ penalty. In fitting the model, we select the tuning parameter using 10-fold cross-validation. The final proportional hazards model includes the selected baseline terms and all time-dependent covariates $L_t$, including indicators of bleeding, haemorrhagic stroke, and left atrial appendage procedures associated with permanent discontinuation and outcomes. To build a model for $\lambda_C(t \mid \mathcal{P}_t)$ in (10), we consider the same procedure for $\lambda_V(t \mid \mathcal{P}_t)$. This is because the decision to re-start treatment was left to the patient and physician, and the resulting censoring may depend on the patient’s characteristics and evolving disease status. To estimate $E\{U(\psi) \mid \mathcal{H}_0\}$, we regress $\tilde{K}_C (T \mid \mathcal{H}_T)^{-1} \Delta U(\psi)$ on $X$ with a $l_1$ penalty.