A Robust Instrumental Variable Method Accounting for Treatment Switching in Open-Label Randomized Controlled Trials

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Abstract

In a randomized controlled trial, treatment switching (also called contamination or crossover) occurs when a patient initially assigned to one treatment arm changes to another arm during the course of follow-up. Overlooking treatment switching might substantially bias the evaluation of treatment efficacy or safety. To account for treatment switching, instrumental variable (IV) methods by leveraging the initial randomized assignment as an IV serve as natural adjustment methods because they allow dependent treatment switching possibly due to underlying prognoses. However, the “exclusion restriction” assumption for IV methods, which requires the initial randomization to have no direct effect on the outcome, remains questionable, especially for open-label trials. We propose a robust instrumental variable estimator circumventing such a caveat. We derive large-sample properties of our proposed estimator, along with inferential tools. We conduct extensive simulations to examine the finite performance of our estimator and its associated inferential tools. An R package “ivsacim” implementing all proposed methods is freely available on R CRAN. We apply the estimator to evaluate the treatment effect of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) on a safety outcome in the Optimized Treatment That Includes or Omits NRTIs trial.

Keywords: Treatment switching; Open-label; G-estimation; Instrumental variable; Exclusion restriction.

1 Introduction

Randomized controlled trials (RCTs) remain as the golden standard for treatment effect evaluation because the randomization guarantees that subjects within different treatment groups are exchangeable. However, even under an RCT, such exchangeability might be contaminated due to treatment switching (also called contamination or crossover) after initial randomization, that
is, when a patient randomized to one treatment arm changes to another arm during the course of follow-up (Cuzick et al. 1997, Demetri et al. 2006, Motzer et al. 2008, Morden et al. 2011, Tsiatis & Davidian 2021). Treatment switching may happen when patients in the control arm switch to the experimental treatment which has manifested short-term effect, in the hope of improving prognosis. It can also occur due to changes in treatment guidelines, whereby treatment options might change during the course of follow-up. Treatment switching might bias the overall survival and the intent-to-treat effect. Inaccurate cost-effectiveness estimates caused by not appropriately handling treatment switching may result, and finite healthcare resources may be wasted.

Traditional methods (Robins 1998, Robins & Finkelstein 2000, Latimer et al. 2017, Jimenez et al. 2017, Latimer et al. 2018, Sullivan et al. 2020) to deal with treatment switching hinge heavily on a “no unmeasured confounding (NUC)” assumption that the treatment switching process is random through time, possibly conditional on measured baseline or time-varying characteristics. Unfortunately, NUC is unrealistic and tends to fail due to dependence between the switching process and the outcome of interest upon unknown factors because even under the sharp null hypothesis of no treatment effect, patients who switch treatment tend to have a different prognosis than patients who remain on their originally assigned treatment.

To overcome unmeasured confounding, instrumental variables (IV) methods (Angrist et al. 1996, Angrist & Krueger 2001, Wooldridge 2010, Martinussen et al. 2017) were carefully designed. An IV is a pre-treatment variable known to be associated with the treatment variable (IV relevance), to only affect the outcome through its effects on the treatment (IV exclusion restriction), and to otherwise be independent of any unmeasured confounders (IV independence). In randomized trials, the initial randomized treatment assignment can be readily leveraged as an IV because IV relevance and IV independence naturally hold. IV exclusion restriction is also reasonable, at least under double-blinded trials. For randomized trials with censored time-to-event outcomes in the presence of treatment switching, IV approaches include, for instance, the rank-preserving structural failure time model (RPSFTM) of Robins & Tsiatis (1991), the structural cumulative failure time model (SCFTM) of (Shi et al. 2021), and the structural cumulative survival model (SCSM) of Ying & Tchetgen Tchetgen (2022). See Ying & Tchetgen Tchetgen (2022) for a comparison of these IV approaches. All aforementioned IV methods rely heavily on three IV assumptions listed above, among which the exclusion restriction might fail to hold under an open-label trial when
site investigators and participants knew the treatment assignments. This is because one cannot rule out the possibility that study physicians might modify a patient’s treatment course as a result of their randomized treatment assignments in a manner that may in turn directly impact the outcome in view, or patients might change their health-seeking behavior after treatment assignment. These induce an unintended direct effect of the randomized treatment on the outcome and hence violate the exclusion restriction assumption of an IV. Such acknowledgment invalidates all causal claims on the basis of the IV methods above.

In this paper, we propose an instrumental variable estimator to handle treatment switching under a structural cumulative survival model without assuming exclusion restriction. Instead, we adapt the “no interaction with unmeasured selection” assumption proposed in Tchetgen Tchetgen et al. (2021) to the time-varying treatment process. Our estimator allows for a time-varying treatment effect and we further develop an asymptotic framework for inference. We evaluate the proposed estimator’s finite-sample performance via extensive simulations. The proposed estimator and inferential tools are implemented in the freely available R package “ivsacim” (Ying 2022) on R CRAN. We apply the proposed approach to evaluate the exposure effect of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) on a key safety outcome (time to first severe or worse sign or symptom) in participants receiving a new antiretroviral regimen that omitted or added NRTIs in the open-label Optimized Treatment That Includes or Omits NRTIs (OPTIONS) trial (Tashima et al. 2015).

We give a preview of the data we aim to analyze since throughout the paper we constantly refer to it. The Optimized Treatment That Includes or Omits NRTIs trial was a multicenter, open-label, prospective, randomized, controlled study evaluating the benefits and risks of omitting versus adding NRTIs to a new optimized antiretroviral regimen for HIV-infected patients. Participants were randomly assigned either to omit or to add NRTIs after choosing an optimized regimen and an NRTI regimen. Treatment switching was present in this trial due to the potential discontinuation of NRTI assignment, which occurred when a participant in the omit-NRTIs group started any NRTIs or when a participant in the add-NRTIs group failed to initiate or permanently discontinued all NRTIs. Therefore, both directions of treatment switching could occur. Ying & Tchetgen Tchetgen (2022) investigated the treatment effect on a safety outcome, the time to first severe or worse sign or symptom, under their SCSM leveraging initial randomized as an IV, assuming the exclu-
sion restriction. However, a caveat here is that the OPTIONS trial was open-label, that is, site investigators and participants knew the treatment assignments. This might lead to the violation of the exclusion restriction, thus invalidating their analysis, which has motivated our study to alleviate such concern by proposing a robust IV method and reanalyzing the OPTIONS trial without assuming the exclusion restriction.

The remainder of the article is organized as follows. We introduce notation, structural cumulative survival models, and assumptions in Section 2. In Section 3, we construct a recursive estimator under the SCSM and assumptions listed in Section 2. We conduct extensive simulations to evaluate finite-sample performance of our estimator in Section 4 and we apply our proposed estimator to reanalyze the OPTIONS trial in Section 5. Proofs and additional theoretical results are provided in the appendix.

2 Preliminaries

Define

- \( T \), a time to event outcome of interest, \( C \), potential censoring time, \( X = \min (T, C) \), a subject’s censored event time, and \( \Delta = 1 (T \leq C) \), a subject’s observed event indicator;
- We introduce the counting process notation. We write \( N(t) = \mathbb{1}(X \leq t, \Delta = 1) \) and \( Y(t) = \mathbb{1}(X \geq t) \) as the observed counting process and the associated at-risk processes;
- We assume that recorded data on treatment do not change except at discrete times \( \{1, \cdots, M\} \). Thus the time-varying treatment \( D(m) = 1 \) if subject \( i \) is treated or exposed at time \( m \), 0 otherwise. We write \( \bar{D}(m) = \{D(l) : 1 \leq l \leq m\} \). For any \( m > X \), \( D(m) \) is not observed. We define \( D(m) = 0 \) for \( m > X \), so that the whole treatment process is well defined for each subject even after the outcome event has occurred. Here we assume treatment is binary only to facilitate exposition and suit our data application. Our framework can accommodate any treatment structure like multi-level and continuous;
- \( Z \) denotes the instrumental variable corresponding to the randomized treatment assignment in a randomized trial;
• We define $T\{\bar{d}(m), 0, z\}$, the potential time to event had possibly contrary to fact, the subject been assigned to treatment $z$, followed the treatment regime $\bar{d}(m)$ up to time $m$ and the control treatment thereafter. We make the consistency assumption that $T = T\{\bar{d}(m), 0, z\}$ with probability one for individuals with observed $\bar{D}(m) = \bar{d}(m)$, $D(l) = 0$, for $l > m$, and $Z = z$. We further assume that intervening on exposure can only affect survival after the time of that exposure, in other words, the event $T\{\bar{D}(m-1), 0, Z\} \geq m$ occurs if and only if the event $T\{\bar{D}(l), 0, Z\} \geq m$ also occurs for all $l \geq m$. It follows that $\{T \geq t\}$ and $\{T\{\bar{D}(m), 0, Z\} \geq t\}$ are the same events for $t \in [m, m+1)$.

We later propose an instrumental variable estimator under the handle treatment switching under a structural cumulative survival model (SCSM) without assuming exclusion restriction. We first introduce SCSMs. An SCSM imposes models on the negative log-ratio $\gamma_m\{t; \bar{D}(m), Z\}$ of two counterfactual survival probabilities at time $t$ under treatment strategies that differ only at time $m$ for each time $m < t$, or equivalently

$$
\exp \left[ -\gamma_m\{t; \bar{D}(m), Z\} \right] = \frac{\mathbb{P}[T\{\bar{D}(m), 0, Z\} > t|\bar{D}(m), Z, T \geq m]}{\mathbb{P}[T\{\bar{D}(m-1), 0, z = 0\} > t|\bar{D}(m), Z, T \geq m]},
$$

for any $t \geq m$. An SCSM therefore may be interpreted as encoding for individuals still at risk for the outcome at time $m$ with covariates, IV and treatment history $Z, \bar{D}(m)$, the ratio of survival probabilities of remaining event-free at time $t \geq m$ upon receiving one final blip of treatment at time $m - 1$ versus at time $m$.

We prefer SCSMs over the rank-preserving structural failure time models (RPSFTMs) (Robins & Tsiatis 1991) and structural cumulative failure time models (SCFTMs) (Shi et al. 2021). This is because estimation under RPSFTMs requires artificial censoring to address administrative censoring, which can further increase bias, aggravate efficiency loss, and render estimation computationally challenging (Robins & Tsiatis 1991, Joffe 2001, Joffe et al. 2012, Vansteelandt et al. 2014, Latimer et al. 2019). On the other hand, SCSMs do not require artificial censoring because it operates on cumulative survival models rather than directly dealing with actual survival times. Another important advantage of SCSMs is that the estimators based on SCSMs typically have a closed form via a recursive solution and therefore are guaranteed to exist. In contrast, the proposed estimating equation under both RPSFTMs and SCFTMs may not admit a solution, even when it does, such a solution may not be uniquely defined.
We choose to assume
\[ \gamma_m(t; \bar{D}(m), Z) = \gamma_m(m+1; D(m), Z) = \int_t^{\infty} D(m) dB_D(s) + Z dB_Z(s). \] \hspace{1cm} (1)

This posits:

1. The negative log-ratio \( \gamma_m\{t; \bar{D}(m), Z\} \) is encoded by two parameters \( B_D(t) \) and \( B_Z(t) \) capturing the actual treatment effect by \( \bar{D}(t) \) and the direct effect of the knowledge of the treatment assignment \( Z \), respectively. Allowing \( B_Z(t) \) to exist is one main contribution of this paper.

2. The effect is allowed to vary across time nonparametrically, which is flexible to capture the possible time-varying effects of \( \bar{D} \) and \( Z \);

3. The effect at time \( m \) is short-lived in the sense that \( \gamma_m(t; \bar{D}(m), Z) = \gamma_m(m+1; D(m), Z) \) for all \( t \geq m + 1 \), in other words, only the treatment \( D(m) \) at time \( m \) can modify the survival between \( [m, m+1) \). This assumption is needed for identification given only one instrument, which was also assumed in Ying & Tchetgen Tchetgen (2022), Shi et al. (2021), Robins & Tsiatis (1991).

Besides being interpreted as a ratio of conditional survival probabilities, the model specification by (1) delivers another convenient interpretation of the contrast of the marginal survival functions, with an additional condition of no-current treatment value interaction Robins & Greenland (1994),

\[
\frac{\mathbb{P} \left[ \{T_\{\bar{D}(m-1), d(m), 0, Z\} > t|\bar{D}(m-1), D(m) = d(m), Z, T \geq m\} \right]}{\mathbb{P} \left[ \{T_\{\bar{D}(m-1), d(m), 0, Z\} > t|\bar{D}(m-1), D(m) = d(m), Z, T \geq m\} \right]} = \frac{\mathbb{P} \left[ \{T_\{\bar{D}(m-1), d(m), 0, Z\} > t|\bar{D}(m-1), D(m) = 0, Z = 0, T \geq m\} \right]}{\mathbb{P} \left[ \{T_\{\bar{D}(m-1), d(m), 0, Z\} > t|\bar{D}(m-1), D(m) = 0, Z = 0, T \geq m\} \right]}. \hspace{2cm} (2)
\]

It essentially states that the instantaneous causal effect of one final blip of treatment at time \( m \) among individuals who were treated at time \( m \) is equal to that among individuals who were not treated at time \( m \) conditional on past history. In fact, under (1) and the no-current treatment value interaction condition (2), one can show that

\[
\frac{\mathbb{P} \left\{ T(d = 1, z > t) \right\}}{\mathbb{P} \left\{ T(d = 0, z > t) \right\}} = \exp \left\{ - \int_0^t dB_D(s) \right\} = \exp \left\{ - B_D(t) \right\}.
\]
Therefore our estimand $B_D(t)$ can be interpreted as the difference in the log-marginal cumulative intensity function comparing always-treated versus never-treated regimes up to time $t$ with all subjects randomized to either treatment or control, which encodes the causal effect of interest, that is, the causal effect of treatment received. Also, we have

$$P\{T(\bar{d}, z = 1) > t\} = \exp\left\{-\int_0^t 1dB_Z(s)\right\} = \exp\{-B_Z(t)\},$$

where $B_Z(t)$ can be interpreted as the controlled direct effect (VanderWeele 2011, Pearl 2022) of the knowledge of the treatment assignment by clinicians and patients on the outcome.

As a special case of this model specification (1) and often is of interest, one may further impose that the treatment effects are constant as a function of the timing of the final treatment blip, that is, setting

$$\gamma_m\{t; \bar{D}(m), Z\} = \beta_D D(m)(t - m) + \beta_Z Z(t - m),$$

which later we refer to as the “constant hazards difference model”. This model encodes the SCSM analog of the “common treatment effect” assumption of the rank preserving structural failure time models (Robins & Tsiatis 1991), which states that the treatment effect is the same for all individuals (with respect to time spent on treatment) regardless of when treatment is received.

Note that both SCSMs (1) and (3) described above are guaranteed to be correctly specified under the null hypothesis of no treatment effect, an appealing robustness property of the proposed framework.

Our proposed strategy leverages the randomization process as an instrumental variable satisfying two key standard IV assumptions, but not the exclusion restriction:

**Assumption 1** (IV relevance). *The instrument is associated with the exposure at m for individuals still at risk for the event time for all m; specifically,*

$$Z \not\perp D(m) \mid T \geq m, D(m - 1).$$

IV relevance requires that for subjects who remain at risk for the outcome event at time $m$, the instrument remains predictive of current treatment status even after conditioning on treatment and covariate history. This is typically a reasonable assumption in a randomized trial, given that individuals randomized to the active arm are more likely than in the control arm to be treated over time, even upon conditioning on their history.
**Assumption 2 (IV independence).** The instrument variable is independent of the potential outcome under no treatment,

\[
Z \perp T(\bar{d} = 0, z = 0).
\]

IV independence ensures that the initial randomization itself is unconfounded, which is apparently satisfied in a randomized trial, no matter double-blinded or open-label.

For completeness, here we introduce the exclusion restriction typically assumed in the IV literature that we do not impose. The exclusion restriction assumes that \( T(\bar{d}, z) = T(\bar{d}) \), which rules out the possibility that randomization itself can impact the outcome via a pathway not involving treatment actually taken. However, as we mentioned earlier, this assumption is inclined to fail in an open-label randomized trial, as the knowledge of assigned treatment may change clinicians’ treatment guidelines or patients’ health-seeking behavior, which in turn influences the outcome. Ying & Tchetgen Tchetgen (2022) not only imposed model (1), Assumptions 1, 2 but also assumed the exclusion restriction and set \( B_Z(t) \equiv 0 \) in (1), leading to

\[
\frac{\mathbb{P}[T\{\bar{D}(m), 0\} > t|\bar{D}(m), Z, T \geq m]}{\mathbb{P}[T\{\bar{D}(m - 1), 0\} > t|\bar{D}(m), Z, T \geq m]} = \exp \left[ - \int_{m}^{t \wedge (m+1)} D(m) dB_D(s) \right], \tag{4}
\]

which asserts that the instrument \( Z \) does not modify the effect of the treatment \( \bar{D}(m) \) on the outcome \( T \) on the multiplicative scale. We, however, do not assume them.

The relaxation of the exclusion restriction leads to another unknown parameter \( B_Z(t) \) compared to that in Ying & Tchetgen Tchetgen (2022) which requires an additional estimating equation to identify. Inspired by Tchetgen Tchetgen et al. (2021), we impose the following assumption leveraging the treatment process as:

**Assumption 3 (IV No Interaction with Unmeasured Confounders).** We assume the treatment process satisfies

\[
\mathbb{E}\{D(t)|Z, T(\bar{d} = 0, z = 0)\} = \alpha_1(t; Z) + \alpha_2\{t; T(\bar{d} = 0, z = 0)\}.
\]

Such a linear model for treatment process with no interaction between \( Z \) and \( T(\bar{d} = 0, z = 0) \) is typically assumed in IV literature (Li et al. 2015, Tchetgen Tchetgen et al. 2015, Ying et al. 2019), where they introduced an unknown confounder \( U \) for convenience, playing a similar role here as \( T(\bar{d} = 0, z = 0) \).

We make a standard conditional independent censoring assumption.
Assumption 4 (Conditional independent censoring).

\[ C \perp (T, \bar{D}(t), Z). \]

This censoring assumption simplifies estimation so that we can concentrate on dealing with treatment switching. Note that although not further pursued here, the above assumption can be relaxed substantially by only requiring that \( C \perp T \mid \bar{D}(m), Z, X \geq m \). This, on the other hand, requires further adjustment for dependent censoring possibly by standard inverse probability censoring weighting.

3 Estimation

Suppose we observe \( n \) independent and identically distributed samples. Define \( E \) and \( E_n \) as the population mean and the empirical mean. Also we write \( Z^c \) as \( Z - E_n(Z) \) and \( D(t)^c \) as \( D(t) - E_n\{D(t)\mid Z\} \). \( E_n\{D(t)\mid Z\} \) is nonparametric because \( Z \) is binary. We construct an explicit and recursive estimator

\[
\begin{pmatrix}
\hat{B}_D(t) \\
\hat{B}_Z(t)
\end{pmatrix} = \int_0^t \{\hat{M}(s)\}^\dagger E_n \left[ \begin{pmatrix}
Z^cD(s) \\
Z^cD(s)^cD(s)
\end{pmatrix} e^{\int_0^s - D(u)d\hat{B}_D(u) + Zd\hat{B}_Z(u)} dN(s) \right],
\]

where

\[
\hat{M}(s) = E_n \left[ \begin{pmatrix}
Z^cD(s) & Z^cD(s)^cD(s) \\
Z^cZ & Z^cD(s)^cZ
\end{pmatrix} Y(s)e^{\int_0^s - D(u)d\hat{B}_D(u) + Zd\hat{B}_Z(u)} \right],
\]

and \((\cdot)^\dagger\) denotes the Moore-Penrose generalized inverse. Because of the recursive structure of \( \hat{B}(t) \) in (5), and the key fact that the estimator only changes values at observed event times, we may evaluate it forward in time, with initial value \( \hat{B}_D(0) = \hat{B}_Z(0) = 0 \).

We also propose an estimator under the constant hazards difference model (3), where one may use

\[
\hat{\beta}_D = \int_0^\tau w(t) d\hat{B}_D(t), \quad \hat{\beta}_Z = \int_0^\tau w(t) d\hat{B}_Z(t),
\]

with \( w(t) = \tilde{w}(t)/ \int_0^\tau \tilde{w}(s) ds, \tilde{w}(t) = E_n\{Y(t)\} \), and \( \tau \) denoting time of end of study. Note that although all theorems below are built for \( \hat{B}_D(t) \), they can be immediately translated for \( \hat{\beta}_D \) by Slutsky’s theorem and the functional Delta method, which we omit the details.
Theorem 1. Under model (1), Assumptions 1 - 4, and regularity Assumptions 5 - 6 in the appendix, the estimator $(\hat{B}_D(t), \hat{B}_Z(t))$ is uniformly consistent for $B_D(t)$ on $[0, \tau]$, namely,

$$\sup_{t \in [0,\tau]} \left| (\hat{B}_D(t), \hat{B}_Z(t)) - (B_D(t), B_Z(t)) \right| \to 0 \text{ a.s.}$$

The normalized process

$$\sqrt{n}\{(\hat{B}_D(t), \hat{B}_Z(t)) - (B_D(t), B_Z(t))\}$$

converges weakly to a two-dimensional zero-mean Gaussian process.

We postpone the analytic variance estimate of the asymptotic Gaussian process to the appendix due to its complicated structure. Nonetheless, we have implemented our estimator together with its inferential tools into the R package named “ivsacim” (Ying 2022) freely available on R CRAN. Inferential tools include estimate of standard deviations, Z-values, P-values, a goodness-of-fit test for the constant hazards difference model (3) ($H_0 : B_D(t) = \beta_D t$ for all $t$) and as well as for the causal null hypothesis ($H_0 : B_D(t) \equiv 0$ for all $t$).

4 Simulation

Aims: To investigate the finite-sample performance of our proposed estimators $\hat{B}_D(t)$ in (5) and $\hat{\beta}_D$ in (6) which are of primary interest.

Data-generating mechanisms: In order to investigate the finite sample performance of our proposed methods, we conduct a simulation study in which we generate $B = 1000$ data sets of i.i.d data with sample size $N = 1600, 3200$. We generate a bivariate baseline variable $U$ which confounds the relationship between time-varying treatment and the time-to-event outcome:

$$U = (U_1, U_2)\sim \mathcal{N}\left\{\begin{pmatrix} 3/2 \\ 3/2 \end{pmatrix}, \begin{pmatrix} 1/4 & -1/6 \\ -1/6 & 1/4 \end{pmatrix}\right\}.$$

We simulate a scenario in which initial treatment assignment $Z$ is generated as an independent Bernoulli random variable with event probability $\mathbb{P}(Z = 1) = 0.5$. We also generate a potential treatment switching time $W$ for each individual according to

$$\mathbb{P}(W > t|Z,U) = \exp(-0.5t) + Z\{1-\exp(-0.05t)\} + (2Z-1)\{1-\exp(-0.05t-0.1\cdot U_1 t)\}, \ (7)$$
and discretize it into a grid with step size $= 0.1$. A subject experiences treatment $Z$ before $W$ and is switched to $1 - Z$ right after $W$. Thus, $Z$ and $W$ determine a patient’s entire treatment process $\bar{D}$. By (7) we also allow both directions of treatment switching, which fits our application setting. The potential time to event $\tilde{T}(d)$ is generated according to

$$\mathbb{P}\{\tilde{T}(d, z) > t | U\} = \exp \left\{-0.1 \cdot t - 0.2 \cdot \int_0^t d(s) ds - 0.15 \cdot U_2 \cdot t\right\},$$

and the observed time to event $T$ is thus generated via consistency with $\bar{D}$. Independent censoring was then generated with an overall rate of 18%. Treatment switching occurred at an approximate rate of 14%. In the appendix, we confirm that under the proposed data generating mechanism, (1) and Assumption 2-4 hold. Indeed, one can show that (1) holds as

$$\frac{\mathbb{P}\{\tilde{T}(D(m), 0, Z) > t | D(m), Z, \bar{T} > m\}}{\mathbb{P}\{T(D(m-1), 0, z = 0) > t | D(m), Z, \bar{T} > m\}} = \exp \left\{-0.2 \cdot \int_m^{t\wedge(m+1)} D(s) ds - 0.1 \cdot \int_m^{t\wedge(m+1)} Z ds\right\}.$$

**Estimands:** Our estimands are the SCSM treatment effect $B_D(t) = 0.2t$ and the constant hazards difference effect $\beta_D = 0.2$.

**Methods:** Each simulated dataset is analyzed using $\hat{B}_D(t)$ in (5) and $\hat{\beta}_D$ in (6). As a comparison, we also fit the time-varying treatment effect estimator $\hat{B}_{D,YTT}(t)$ and the constant effect estimator $\hat{\beta}_{D,YTT}$ in Ying & Tchetgen Tchetgen (2022) assuming (4) and the exclusion restriction were to hold. $\hat{B}_{D,YTT}(t)$ and $\hat{\beta}_{D,YTT}$ are expected to be biased.

**Performance measures:** We report bias, empirical standard errors (SEE), average estimated standard errors (SD), and coverage probabilities of 95% confidence intervals of both $\hat{B}_D$ and $\hat{B}_{D,YTT}$ at time $t = 1, 2, 3$, also $\hat{\beta}_D$, $\hat{\beta}_{D,YTT}$.

Simulation results concerning $\hat{B}_D(t)$ (5) and $\hat{\beta}_D$ (6) are given in Table 1. Simulation results concerning $\hat{B}_{D,YTT}(t)$ (5) and $\hat{\beta}_{D,YTT}$ (6) are given in Table 2. The results confirm that the proposed estimator $\hat{B}_D(t)$ has small biases both at sample sizes 1600 and 3200 at $t = 1, 2, 3$. The estimated standard errors match Monte Carlo standard errors and overall 95% confidence intervals attain the nominal levels among sample sizes 1600 and 3200 at $t = 1, 2, 3$. It is seen from the simulation that the estimator $\hat{\beta}_D$ is consistent and that the variability is well estimated, leading to satisfactory coverage probabilities. Ying & Tchetgen Tchetgen (2022) has shown its method failed under a violation of exclusion restriction in its appendix. Here, our simulation once again confirmed
this. In fact, \( \hat{B}_{D,YTT}(t) \) is severely biased regardless of the sample size, especially when \( t = 2, 3 \). This is because more subjects switch their treatment and the direct effect of the initial treatment assignment starts to influence the estimator. The coverage rates of \( \hat{B}_{D,YTT}(t) \) fail to attain the nominal level due to biases. The same situation applies to \( \hat{\beta}_{D,YTT} \) as well.

Table 1: Simulation results for the SCSM treatment effect model \( \hat{B}_D(t) \) and the constant hazards difference model \( \hat{\beta}_D \). Bias of \( \hat{B}_D(t) \), empirical standard error, see(\( \hat{B}_D(t) \)), average estimated standard error, sd(\( \hat{B}_D(t) \)), and coverage probability of 95% confidence intervals CP(\( \hat{B}_D(t) \)), 95% CP(\( \hat{B}_D(t) \)), at time \( t = 1, 2, 3 \), bias of \( \hat{\beta}_D \), empirical standard error, see(\( \hat{\beta}_D \)), average estimated standard error, sd(\( \hat{\beta}_D \)), and coverage probability of 95% pointwise confidence intervals CP(\( \hat{\beta}_D \)), 95% CP(\( \hat{\beta}_D \)), for sample size \( N = 1600, 3200 \) and \( R = 1000 \) Monte Carlo samples.

| Sample Sizes | t = 1 | t = 2 | t = 3 | t = 1 | t = 2 | t = 3 |
|--------------|-------|-------|-------|-------|-------|-------|
| N = 1600     | Bias(\( \hat{B}_D(t) \)) | -0.0186 | -0.0233 | -0.0167 | Bias(\( \hat{\beta}_D \)) | -0.0058 |
|              | SEE(\( \hat{B}_D(t) \))  | 0.0918  | 0.1141  | 0.1734  | see(\( \hat{\beta}_D \)) | 0.0591  |
|              | SD(\( \hat{B}_D(t) \))   | 0.1125  | 0.1526  | 0.2223  | sd(\( \hat{\beta}_D \)) | 0.0738  |
|              | 95% CP(\( \hat{B}_D(t) \))| 94.0    | 96.8    | 96.5    | 95% CP(\( \hat{\beta}_D \)) | 95.3    |
| N = 3200     | Bias(\( \hat{B}_D(t) \)) | -0.0133 | -0.0140 | -0.0145 | Bias(\( \hat{\beta}_D \)) | -0.0064 |
|              | SEE(\( \hat{B}_D(t) \))  | 0.0623  | 0.0852  | 0.1331  | see(\( \hat{\beta}_D \)) | 0.0441  |
|              | SD(\( \hat{B}_D(t) \))   | 0.0781  | 0.1051  | 0.1556  | sd(\( \hat{\beta}_D \)) | 0.0515  |
|              | 95% CP(\( \hat{B}_D(t) \))| 95.3    | 95.8    | 95.5    | 95% CP(\( \hat{\beta}_D \)) | 95.9    |
Table 2: Simulation results for the SCSM treatment effect model $\hat{B}_{D,YTT}(t)$ and the constant hazards difference model $\hat{\beta}_{D,YTT}$. Bias of $\hat{B}_{D,YTT}(t)$, empirical standard error, see($\hat{B}_{D,YTT}(t)$), average estimated standard error, sd($\hat{B}_{D,YTT}(t)$), and coverage probability of 95% confidence intervals CP($\hat{B}_{D,YTT}(t)$), 95% CP($\hat{B}_{D,YTT}(t)$), at time $t = 1, 2, 3$, bias of $\hat{\beta}_{D,YTT}$, empirical standard error, see($\hat{\beta}_{D,YTT}$), average estimated standard error, sd($\hat{\beta}_{D,YTT}$), and coverage probability of 95% pointwise confidence intervals CP($\hat{\beta}_{D,YTT}$), 95% CP($\hat{\beta}_{D,YTT}$), for sample size $N = 1600, 3200$ and $R = 1000$ Monte Carlo samples.

| Sample Sizes | $t = 1$ | $t = 2$ | $t = 3$ | $t = 1$ | $t = 2$ | $t = 3$ |
|--------------|---------|---------|---------|---------|---------|---------|
| $N = 1600$   | Bias($\hat{B}_{D,YTT}(t)$) | 0.0543  | 0.1227  | 0.2185  | Bias($\hat{\beta}_{D,YTT}$) | 0.0704  |
|              | SEE($\hat{B}_{D,YTT}(t)$)  | 0.0385  | 0.0755  | 0.1439  | see($\hat{\beta}_{D,YTT}$) | 0.0387  |
|              | SD($\hat{B}_{D,YTT}(t)$)   | 0.0435  | 0.0861  | 0.1687  | sd($\hat{\beta}_{D,YTT}$) | 0.0451  |
|              | 95% CP($\hat{B}_{D,YTT}(t)$) | 75.9    | 71.9    | 80.0    | 95% CP($\hat{\beta}_{D,YTT}$) | 69.2    |
| $N = 3200$   | Bias($\hat{B}_{D,YTT}(t)$) | 0.0546  | 0.1265  | 0.2241  | Bias($\hat{\beta}_{D,YTT}$) | 0.0723  |
|              | SEE($\hat{B}_{D,YTT}(t)$)  | 0.0261  | 0.0519  | 0.0970  | see($\hat{\beta}_{D,YTT}$) | 0.0271  |
|              | SD($\hat{B}_{D,YTT}(t)$)   | 0.0308  | 0.0608  | 0.1187  | sd($\hat{\beta}_{D,YTT}$) | 0.0317  |
|              | 95% CP($\hat{B}_{D,YTT}(t)$) | 58.7    | 43.5    | 54.3    | 95% CP($\hat{\beta}_{D,YTT}$) | 36.1    |

5 Real Data Application

We aim to reanalyze the treatment effect on a safety outcome, the time to first severe or worse sign or symptom, in the Optimized Treatment That Includes or Omits NRTIs trial as Ying & Tchetgen Tchetgen (2022) did. An introduction of the analysis was given in Section 1. A summary of events and treatment switching in the study can be found in Table 3. Ying & Tchetgen Tchetgen (2022) investigated the treatment effect under their SCSM leveraging initial randomization as an IV, assuming the exclusion restriction. They found a significant time-varying effect of NRTIs on the safety outcome, which revealed possible safety concerns of NRTIs. However, a caveat here is that the OPTIONS trial was open-label, that is, site investigators and participants knew the treatment assignments. This might lead to the violation of the exclusion restriction, thus invalidating their analysis. Therefore, we would like to reanalyze the OPTIONS trial without assuming the
exclusion restriction.

Table 3: A summary of the safety outcome (first severe or worse sign or symptom) and NRTI assignment change (treatment switching) in the OPTIONS trial, compared between treatment groups.

| Patients, n (%) | Difference (95% CI), percentage points |
|-----------------|----------------------------------------|
|                 | Add NRTIs (n = 180) | Omit NRTIs (n = 177) |                  |
| First severe or worse sign or symptom | 51 (28.3) | 35 (19.8) | 8.6 (-0.8 to 17.9) |
| Change in NRTI assignment | 10 (5.3) | 17 (9.5) | -4.0 (-10.1 to 2.0) |
| Change in NRTI assignment before safety outcome failure | 8 (3.4) | 9 (2.8) | -0.6 (-4.4 to 5.4) |

Using the proposed approach to formally account for treatment switching by leveraging randomized treatment assignment as an IV for treatment actually received which is likely confounded by unmeasured factors, we performed a test of the sharp null hypothesis of no individual causal effect, i.e. $B_D(t) = 0$, against which we found nonsignificant statistical evidence, P-value 0.086. Our approach also delivered a nonparametric estimator $\hat{B}_D(t)$ along with 95% pointwise confidence bands displayed at the top left in Figure 1. From the figure, we observe a hazard rate for experiencing the safety outcome severe/worse sign/symptom over time in the add-NRTI group compared to the omit-group. Under a constant hazards difference model (3), our approach estimated a hazards difference of -0.0537 (-0.120, 0.012), P-value 0.109, though there is significant evidence of a time-varying effect, indicated by our goodness-of-fit test rejecting the constant effect model (P-value 0.039). The test of the null hypothesis of no direct causal effect of the randomization, i.e. $B_Z(t) = 0$, reports a nonsignificant P-value 0.08. A nonparametric estimator $\hat{B}_Z(t)$ along with 95% pointwise confidence bands are displayed at the top right in Figure 1.
Figure 1: Top left figure: The step line corresponds to the estimated SCSM treatment effect of NRTIs, $\hat{B}_D(t)$, on the safety outcome (time to first severe or worse sign or symptom), along with 95% pointwise confidence bands. The y-axis corresponds to the estimated SCSM treatment effect at time $t$, namely, $\hat{B}_D(t)$. The curved line corresponds to the constant hazards difference estimator $\hat{\beta}_D$. Top right figure: The step line corresponds to the estimated SCSM direct effect of initial treatment assignment, $\hat{B}_Z(t)$, on the safety outcome, along with 95% pointwise confidence bands. The y-axis corresponds to the estimated SCSM treatment effect at time $t$, namely, $\hat{B}_Z(t)$. The curved line corresponds to the constant hazards difference estimator $\hat{\beta}_Z$. Bottom figure: The step line corresponds to the estimated SCSM total effect of treatment assignment, $\hat{B}_D(t) + \hat{B}_Z(t)$, on the safety outcome, along with 95% pointwise confidence bands. The y-axis corresponds to the estimated SCSM treatment effect at time $t$, namely, $\hat{B}_D(t) + \hat{B}_Z(t)$. The curved line corresponds to the constant hazards difference estimator $\hat{\beta}_D + \hat{\beta}_Z$. 
Ying & Tchetgen Tchetgen (2022) uncovered possible safety concerns of NRTIs, that is, adding NRTIs may increase the risk of severe or worse sign or symptom for HIV-infected patients. Our analysis reveals that such safety concern is possibly caused by the effect of unblinded treatment assignment. Therefore one possible explanation is that knowing treatment assignments had possibly led to a change of treatment courses by the clinicians or health-seeking behavior of treatment-aware patients, which resulted in worse sign or symptom. We also append \( \hat{B}_D(t) + \hat{B}_Z(t) \) along with 95% pointwise confidence bands displayed at the bottom in Figure 1, which indeed shows a similar trend as the real data application in Ying & Tchetgen Tchetgen (2022). One possible explanation is that since Ying & Tchetgen Tchetgen (2022) cannot distinguish the effect of \( D(t) \) and \( Z \) but can only capture the the total effect of treatment actually received and assigned \( B_D(t) + B_Z(t) \) when the no-current treatment value interaction condition (2) holds.

Acknowledgement

The author would like to thank Eric J. Tchetgen Tchetgen for his valuable suggestions for improving the manuscript. The author would also like to thank Dr. Diana Ventura from the Center for Biostatistics in AIDS Research at T.H. Chan School of Public Health at Harvard University for providing us with the raw data for this manuscript.

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A Identification

Indeed, we can show

**Proposition 1.** Under model (1) and Assumptions 1-4, the parameter of interest \((B_D(t), B_Z(t))\)^T solves the following two sequences of population-level estimating equations at each time \(t\),

\[
\mathbb{E}\left[\begin{pmatrix}
Z^c \\
Z^c D(t)^c
\end{pmatrix} e^{\int_0^t D(s)dB_D(s) + ZdB_Z(s)} Y(t) \left\{dN(t) - D(t)dB_D(t) - ZdB_Z(t)\right\}\right] = 0, \quad (8)
\]

where \(Z^c = Z - \mathbb{E}(Z|L)\) and \(D(t)^c = D(t) - \mathbb{E}\{D(t)|Z, L\}\).

However, the above Equation (8) cannot identify \((B_D(t), B_Z(t))\)^T because the design matrix

\[
\mathcal{M}(t) = \mathbb{E}\left[\begin{pmatrix}
Z^c D(t) & Z^c D(t)^c D(t) \\
Z^c Z & Z^c D(t)^c Z
\end{pmatrix} Y(s) \exp\left\{\int_0^s D(u)dB_D(u) + ZdB_Z(u)\right\}\right]. \quad (9)
\]

might be degenerate at some time \(t\). Especially, consider the case when there is indeed no treatment switching, then (9) becomes

\[
\mathcal{M}(t) = \mathbb{E}\left[\begin{pmatrix}
Z^c Z & Z^c Z^c Z \\
Z^c Z & Z^c Z^c Z
\end{pmatrix} Y(s) \exp\left\{\int_0^s D(u)dB_D(u) + ZdB_Z(u)\right\}\right],
\]

which is degenerate. Therefore intuitively the uniqueness of the solutions to (9) necessitates enough rates of treatment switching across \(t \in [0, \tau]\). This kind of assumption can be awkward in practice. Therefore to avoid such an assumption, one may leverage the Moore-Penrose generalized inverse that is commonly adopted in survival analysis literature (Martinussen & Scheike 2006) and impose the following weaker assumption

**Assumption 5.** \((B_D(t), B_Z(t))\)^T is the continuous solution to the equation \(B(t) = \Upsilon(B, t)\) with minimum \(L_2\) norm at each \(t\).

The validity of this regularity assumption is beyond the scope of this statistical paper but can be of interest for researchers on differential equations. With this and Proposition 1, one can show that \((B_D(t), B_Z(t))\)^T admits a closed form solution

\[
\begin{pmatrix}
B_D(t) \\
B_Z(t)
\end{pmatrix} = \int_0^t \left\{\mathcal{M}(s)\right\}^\dagger \mathbb{E}\left[\begin{pmatrix}
Z^c \\
Z^c D(s)^c
\end{pmatrix} \exp\left\{\int_s^t D(u)dB_D(u) + ZdB_Z(u)\right\} dN(s)\right],
\]

21
where $(\cdot)^\dagger$ is the Moore-Penrose generalized inverse.

Note that since (3) is a submodel of (1), this result carries over to that for $(\beta_D, \beta_Z)^\top$ under (1).

B Proofs

B.1 Proof of Proposition 1

We write $\tilde{N}(t) = \mathbb{1}(T \leq t)$ the counting process of event time. It is straightforward that (1) implies

\[
\begin{align*}
\mathbb{E}(d\tilde{N}_{D(m-1),0,\tilde{z}=0}(t)|\bar{D}(m), Z, T_{D(m-1)}, 0, \tilde{z}=0 \geq t) \\
= \mathbb{E}(d\tilde{N}_{D(m),0,\tilde{z}}(t)|D(m), Z, T_{D(m)}, 0 \geq t) \\
- D(m)\mathbb{1}(m \leq t < m+1)dB_D(t) - Z\mathbb{1}(m \leq t < m+1)dB_Z(t).
\end{align*}
\]

(10)
For any time $t$ satisfying $m \leq t < m + 1$, under (10) and Assumption 4,

\[
\mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^t D(s)dB_D(s) + ZdB_Z(s)} Y(t) \left\{ d\tilde{N}(t) - D(m)dB_D(t) - ZdB_Z(t) \right\} \right]
\]

\[
= \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^t D(s)dB_D(s) + ZdB_Z(s)} Y(t) \left\{ d\tilde{N}_{D(m),0}(t) - D(m)dB_D(t) - ZdB_Z(t) \right\} \right]
\]

\[
= \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-} D(s)dB_D(s) + ZdB_Z(s)} Y(t) \left\{ \mathbb{E}(d\tilde{N}_{D(m),0}(t) | \tilde{D}(m), Z, \tilde{T}_{D(m),0} \geq t) - D(m)dB_D(t) - ZdB_Z(t) \right\} \right]
\]

\[
= \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-} D(s)dB_D(s) + ZdB_Z(s)} \mathbb{P}(\tilde{T}(\tilde{D}(m-1),0) \geq t | \tilde{D}(m), Z, \tilde{T}_{D(m),0} \geq t) \mathbb{1}(C \geq t) \right.
\]

\[
\cdot \left. \mathbb{E}(d\tilde{N}_{D(m),0}(t) | \tilde{D}(m), Z, \tilde{T}_{D(m),0} \geq t) - D(m)dB_D(t) - ZdB_Z(t) \right\}
\]

\[
= \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-} D(s)dB_D(s) + ZdB_Z(s)} Y_{\tilde{D}(m-1),0,z=0}(t) \mathbb{1}(C \geq t) \right]
\]

\[
\cdot \left[ \mathbb{E}(d\tilde{N}_{D(m),0}(t) | \tilde{D}(m), Z, \tilde{T}_{D(m),0} \geq t) - D(m)dB_D(t) - ZdB_Z(t) \right]
\]

\[
= \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-} D(s)dB_D(s) + ZdB_Z(s)} Y_{\tilde{D}(m-1),0,z=0}(t) \mathbb{1}(C \geq t) \right]
\]

\[
\cdot \left[ \mathbb{E}(d\tilde{N}_{D(m-1),0,z=0}(t) | \tilde{D}(m), Z, \tilde{T}_{D(m-1),0,z=0} \geq t) \right]
\]

\[
= \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-} D(s)dB_D(s) + ZdB_Z(s)} Y_{\tilde{D}(m-1),0,z=0}(t) \mathbb{1}(C \geq t) \right]
\]

\[
\cdot d\tilde{N}_{D(m-1),0,z=0}(t)
\].
Now we can repeat these steps in order to blip down the effect of treatment $D(m - 1)$ at $m - 1$. However, note that for $m - 1 < t \leq m$, this effect is null by assumption, and $\int_0^{m-1} D(s)dB_D(s)$ is a function of $\bar{D}(m - 1)$. It follows that

\[
E \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-1} D(s)dB_D(s) + ZdB_Z(s)} Y_{\bar{D}(m-1),0,z=0(t)} \mathbb{1}(C \geq t) d\bar{N}_{\bar{D}(m-1),0,z=0(t)} \right] \\
E \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-1} D(s)dB_D(s) + ZdB_Z(s)} Y_{\bar{D}(m-1),0,z=0(t)} \mathbb{1}(C \geq t) \cdot E(d\bar{N}_{\bar{D}(m-1),0,z=0(t)}|\bar{D}(m-1), Z, \hat{T}_{\bar{D}(m-1),0,z=0 \geq t}) \right] \\
E \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-1} D(s)dB_D(s) + ZdB_Z(s)} P(T_{\bar{D}(t_{m-2}),0,z=0 \geq t}|\bar{D}(m-1), Z, \hat{T}_{\bar{D}(m-1),0,z=0 \geq t}) \cdot E(d\bar{N}_{\bar{D}(m-1),0,z=0(t)}|\bar{D}(m-1), Z, \hat{T}_{\bar{D}(m-1),0,z=0 \geq t}) \right] \\
= E \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-1} D(s)dB_D(s) + ZdB_Z(s)} Y_{\bar{D}(t_{m-2}),0,z=0(t)} \mathbb{1}(C \geq t) \right] \\
E(d\bar{N}_{\bar{D}(m-1),0,z=0(t)}|\bar{D}(m-1), Z, \hat{T}_{\bar{D}(m-1),0,z=0 \geq t}) \\
E \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-1} D(s)dB_D(s) + ZdB_Z(s)} Y_{\bar{D}(t_{m-2}),0,z=0(t)} \mathbb{1}(C \geq t) \right] \\
E(d\bar{N}_{\bar{D}(m-2),0,z=0(t)}|\bar{D}(m-1), Z, \hat{T}_{\bar{D}(t_{m-2}),0,z=0 \geq t}) \\
= E \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^{m-1} D(s)dB_D(s) + ZdB_Z(s)} Y_{\bar{D}(t_{m-2}),0,z=0(t)} \mathbb{1}(C \geq t) d\bar{N}_{\bar{D}(t_{m-2}),0(t)} \right].
\]
A recursive application of the above argument yields
\[
\mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} \exp \left( \int_0^{t^-} D(s) dB_D(s) \right) \left[ dN_{D(m),0}(t) - Y(t) D(m) dB_D(t) \right] \right] = \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} Y_{0,z=0}(t) 1(C \geq t) dN_0(t) \right] = \mathbb{E} \left[ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} Y_{0,z=0}(t) dN_{0,z=0}(t) \mathbb{P}(C \geq t|L) \right] = \mathbb{E} \left[ \begin{pmatrix} Z^c Y_0(t) dN_{0,z=0}(t) \mathbb{P}(C \geq t|L) \\ Z^c \alpha_2(t; T(0, z = 0)) Y_0(t) dN_{0,z=0}(t) \mathbb{P}(C \geq t|L) \end{pmatrix} \right] = 0,
\]
by the IV independence assumption. Consequently, (9) holds.

We introduce additional notation, some technical assumptions, and a necessary Helly’s selection theorem to prove Theorem 1. For the proofs below, we plug in the truth $\mathbb{E}(Z|L)$ and $\mathbb{E}(D(t)|Z, L)$ into the estimators. We prove their uniform consistency and asymptotic normality.

For two-step estimators given in the main text with regular and asymptotically linear estimates $\hat{\mathbb{E}}(Z|L)$ and $\hat{\mathbb{E}}(D(t)|Z, L)$, a Taylor expansion can be added into the proofs.

To facilitate exposition, we write $B(t) = (B_D(t), B_Z(t))^\top$. Define
\[
\Upsilon(B, t) = \int_0^t [\mathbb{M}\{B, s\}]^\top \mathbb{E} \left\{ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^t (D(u), Z) dB(u)} dN(s) \right\}.
\]

Note that $B(t)$ is the solution to $B(t) = \Upsilon(B, t)$ by results in the last section.

We write $\|g\|_\infty = \sup_{t \in [0, \tau]} |g(t)|$ and use $\mathcal{V}(g)$ to denote the total variation of $g$ over the interval $[0, \tau]$. Let $M^o = \|B(t)\|_\infty < \infty$. Define
\[
\tilde{\mathbb{M}}(B, s) = \mathbb{E}_n \left\{ \begin{pmatrix} Z^c D(s) \\ Z^c D(s)^c D(s) \\ Z^c Z \\ Z^c D(s)^c Z \end{pmatrix} Y(s) e^{\int_0^s -(D(u), Z) dB(u)} dN(s) \right\},
\]
\[
\Upsilon_n(B, t) = \int_0^t [\tilde{\mathbb{M}}(B, s)]^\top \mathbb{E}_n \left\{ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^t -(D(u), Z) dB(u)} dN(s) \right\},
\]
and
\[
\tilde{\Upsilon}_n(B, t) = \int_0^t [\tilde{\mathbb{M}}(B, s)]^\top \mathbb{E}_n \left\{ \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^t -(D(u), Z) dB(u)} dN(s) \right\}.
\]
We note for later reference that for any two functions $B_1$ and $B_2$,
\[
\|\Upsilon(\xi(B_1), t) - \Upsilon(\xi(B_2), t)\|_\infty \leq 4\tau M_{\text{max}} \exp(M)/\nu \|B_1 - B_2\|_\infty.
\] (43)

The following regularity condition is trivially satisfied for binary $D(t)$ and $Z$.

**Assumption 6.** The instrument $Z$ and the treatment process $D(t)$ is uniformly bounded by $M_{\text{max}}$.

Define
\[
\mathcal{M}(B(\cdot), t) = \mathbb{E} \left\{ \begin{pmatrix} Z^c D(t) & Z^c D(t)^c D(t) \\ Z^c Z & Z^c D(t)^c Z \end{pmatrix} Y(t) e^{\int_0^t \langle D(s), Z \rangle dB(s)} D(t) \right\},
\]
for any $B \in \mathbb{B}$, where $\mathbb{B}$ is the set of two-dimensional functions on $[0, \tau]$ that have total variations bounded by some $M > M^\circ$.

We shall use Helly’s selection theorem to establish Theorem 1.

**Theorem 2** (Helly’s Selection Theorem). Let $\{f_n\}$ be a sequence of functions on $[0, \tau]$ such that $\|f_n\|_\infty \leq A_1$ and $\text{sup}_n \mathcal{V}(f_n) \leq A_2$, where $A_1$ and $A_2$ are finite constants. Then

1. There exists a subsequence $\{f_{n_j}\}$ of $\{f_n\}$ which converges pointwise to some function $f$.

2. If $f$ is continuous, the convergence is uniform.

**Lemma 1.**
\[
\text{sup}_{s \in [0, \tau], B \in \mathbb{B}} |\mathcal{M}(B, s) - \mathcal{M}(B, s)| \to 0 \ a.s.
\]

**Proof.** Define
\[
\phi_{B,s}\{T, \Delta, Z, D\} := \begin{pmatrix} Z^c D(s) & Z^c D(s)^c D(s) \\ Z^c Z & Z^c D(s)^c Z \end{pmatrix} Y(s) e^{\int_0^s \langle D(u), Z \rangle dB(u)}.
\]
Hence $\mathcal{M}(B, s) - \mathcal{M}(B, s) = (\mathbb{P}_n - \mathbb{P}) \phi_{B,s}$. To prove the Lemma it suffices to show that $\{\phi_{B,s} : B \in \mathbb{B}, s \in [0, \tau]\}$ is Gilvenko-Cantelli (Van Der Vaart & Wellner 1996). Note that all functions that are of bounded variation form a Gilvenko-Cantelli class (Van der Vaart 2000, Example 19.11). This is immediate since $\text{max}_{H,s} \mathcal{V}(\phi_{B,s})$ can be proved to be finite easily.
B.2 Proof of Theorem 1

We give a roadmap for the proof of consistency.

1. We construct a modified version $\tilde{B}(t) = \tilde{B}_n(t)$ of the estimator $\hat{B}(t)$ that is uniformly of bounded variation over $n$.

2. We show that

$$\sup_{s \in [0,\tau], B \in \mathcal{B}} |\Upsilon_n(B, s) - \Upsilon(B, s)| \to 0 \text{ a.s.} \quad (44)$$

3. These, together with the Helly’s Selection Theorem, imply $\|\tilde{B}(t) - B(t)\|_{\infty} \to 0$, a.s..

4. Finally we show that $\tilde{B}(t)$ is equal to $\hat{B}(t)$ in large samples, and therefore, $\|\hat{B}(t) - B(t)\|_{\infty} \to 0$, a.s..

STEP 1: Let $\xi(y) = \text{sgn}(y) \min(|y|, M)$. We define the modified estimator $\tilde{B}_n$ to be the solution to the equation $\tilde{B}(t) = \Upsilon_n\{\xi(B), t\}$. Note that by Lemma 1 and Assumption 5, the total variation

$$\mathcal{V}(\tilde{B}) \leq 4\tau M_{\max} \exp(M)/\nu$$

Therefore $\tilde{B}(t)$ is uniformly of bounded variation over $n$. Also, since $\tilde{B}_D(0) = 0$, $\tilde{B}_Z(0) = 0$, $\tilde{B}$ is uniformly bounded, therefore Helly’s selection theorem applies. Note that $\Upsilon\{\xi(B), t\} = \Upsilon(B, t) = B$.

STEP 2: We want to show

$$\sup_{s \in [0,\tau], B \in \mathcal{B}} |\tilde{\Upsilon}_n(B, s) - \Upsilon(B, s)| \to 0, \text{ a.s.}$$

To this end, we first define

$$\psi_{H,t}(T, \Delta, Z, D(\cdot)) := (M(H(\cdot), t))^\dagger \begin{pmatrix} Z^c \\ Z^c D(s)^c \end{pmatrix} e^{\int_0^T (D(s), Z - D(s)) dH(s)} N(t),$$

and therefore $\tilde{\Upsilon}_n(H, t) = \mathbb{E}_n \psi_{H,t}$ and $\Upsilon(H, t) = \mathbb{P} \psi_{H,t}$. Then it suffices to show that $\{\psi_{H,t} : B \in \mathcal{B}, t \in [0, \tau]\}$ is Gilvenko-Cantelli. This result is an immediate consequence of the following facts:
1. All functions that are of bounded variation form a Gilvenko-Cantelli class (Van der Vaart 2000, Example 19.11). Therefore the function class \( \{ (Z^c, Z^c D(s))^{\top} e^{\int_0^s (D(u), Z) d\xi(u)} dH(t) : B \in \mathbb{B}, t \in [0, \tau] \} \) is Gilvenko-Cantelli.

2. A Gilvenko-Cantelli class multiplied by a uniformly bounded, measurable function remains Gilvenko-Cantelli (Van Der Vaart & Wellner 1996, Example 2.10.10).

\[
\sup_{s \in [0, \tau], B \in \mathbb{B}} |\bar{\Upsilon}_n(B, s) - \Upsilon(B, s)| = \|(P_n - P)\psi_H, t\|_\infty \to 0, \text{ a.s.}
\]

Now by Lemma 1,

\[
\sup_{s \in [0, \tau], B \in \mathbb{B}} |\bar{\Upsilon}_n(B, s) - \Upsilon_n(B, s)| \to 0, \text{ a.s.}
\]

These two imply (44).

**STEP 3:** We prove \( \|\bar{B}(t) - B(t)\|_\infty \to 0 \) a.s., by contradiction. Without loss of generality, we assume

\[
\lim_{n \to \infty} \|\bar{B}(t) - B(t)\|_\infty > 0.
\]

By Helly’s Selection Theorem, there exists a subsequence \( \{n_j\} \) such that \( \bar{B}_{n_j}(t) - B(t) \) converges to some limit \( H(t) \). We further claim this limit is continuous, in fact, Lipschitz continuous. To see this, for any \( t_1 < t_2 \) in \( [0, \tau] \), when \( n_j \) is large enough

\[
|B(t_2) - B(t_1)| \leq |B(t_2) - \bar{B}_{n_j}(t_2)| + |\bar{B}_{n_j}(t_2) - \bar{B}_{n_j}(t_1)|
\]

\[
+ |\bar{B}_{n_j}(t_1) - B(t_1)|
\]

\[
\leq \left| \int_{t_1}^{t_2} (\hat{M}(s))^{\top} E_{n_j} \left( \begin{array}{c} Z^c \\ Z^c D(s)^c \end{array} \right) e^{\int_{0}^{s} (D(u), Z) d\xi(\bar{B}_{n_j}(u))} dN(s) \right| + 2\varepsilon
\]

\[
\leq 4M_{\max} \exp(M)/\nu(t_2 - t_1) + 2\varepsilon,
\]

for any \( \varepsilon > 0 \). Therefore, by the second part of Helly’s theorem, the convergence of the subsequence is uniform. Going further, the limit \( B \) satisfies \( B(t) = \Upsilon(B, t) \) since

\[
\|B(t) - \Upsilon(\xi(B), t)\|_\infty \leq \|B(t) - \bar{B}_{n_j}(t)\|_\infty + \|\bar{B}_{n_j}(t) - \Upsilon_n(\xi(\bar{B}_{n_j}), t)\|_\infty
\]

\[
+ \|\Upsilon_n(\xi(\bar{B}_{n_j}), t) - \Upsilon(B, t)\|_\infty + \|\Upsilon(\xi(\bar{B}_{n_j}), t) - \Upsilon(B, t)\|_\infty
\]

\[
\to 0,
\]

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where the last statement results from the uniform convergence of $\tilde{B}_{n_j}(t)$, the definition of $\tilde{B}_{n_j}(t)$, (44) and (43). The fact that the solution $B$ to $B(t) = \Upsilon(B, t)$ is unique by Assumption 5 leads to a contradiction. It hence follows that $\|\tilde{B}(t) - B(t)\|_\infty \to 0$ a.s..

**STEP 4:** Since $\|B(t)\|_\infty \leq M$ and we just showed $\|\tilde{B}(t) - B(t)\|_\infty \to 0$ a.s., for sufficiently large $n$ we have $\|\tilde{B}(t)\|_\infty \leq M + \frac{1}{2}(M - M^\circ) < M$. Therefore, for sufficiently large $n$, $\tilde{B}(t)$ satisfies $\tilde{B}(t) = \Upsilon\{\xi(\tilde{B}), t\} = \Upsilon(\tilde{B}, t)$, or in other words, $\tilde{B}(t) = \tilde{B}(t)$. We thus have $\sup_{t \in [0, \tau]} |\tilde{B}(t) - B(t)| \to 0$, a.s.

The consistency of $(\tilde{B}_D(t, \hat{\theta}), \tilde{B}_Z(t, \hat{\theta}))^\top$ then follows immediately by a Taylor series expansion since $\hat{\theta}$ is consistent for $\theta$.

For asymptotic normality, we aim to provide a sum of i.i.d. representation of $\sqrt{n}\{\tilde{B}(t, \theta) - B(t, \theta)\}$ heuristically. To that end, we rewrite the normalized residual

$$V_n(t, \theta) := \sqrt{n}\{\tilde{B}(t, \theta) - B(t, \theta)\}$$

at a fixed $\theta$ as a solution to a Volterra equation, which shall yield a sum of i.i.d. representation at each time point $t$ in this case. To establish this, we integrate by part the Riemann–Stieltjes integral (the integral is interpreted pathwise for the Càdlàg stochastic process $D_i(s)$, $B_D$ and $B_Z$ are assumed to be continuous),

$$\int_0^{s-} (D_i(u), Z_i)dB(u) = (D_i(s), Z_i)B(s-) - \int_0^{s-} B(u)d(D_i(u), Z_i)^\top$$

$$= (D_i(s), Z_i)B(s-) - \int_0^{s-} B_D(u)dD_i(u)$$

$$=: G_{1,i}(s-) + G_{2,i}(s-).$$

(45)

By Theorem 1 and an application of Slutsky’s Theorem, we can write

$$V_n(t, \theta) = \frac{1}{\sqrt{n}} \int_0^t \sum_{i=1}^n H_i(s, \tilde{B})\{dN_i(s) - (D_i(s), Z_i)dB(s, \theta)\} + o_p(1),$$

where

$$H_i(s, B) := \{M(s)\}^\top(Z_i^c, Z_iD_i^c(s))^\top \exp \left\{ \int_0^{s-} (D_i(u), Z)d\tilde{B}(u, \theta) \right\}.$$ 

Now we are ready to write down the Volterra equation. By consistency and a Taylor expansion,
it is easy to see that
\[ V_n(t, \theta) = \frac{1}{\sqrt{n}} \int_0^t \sum_{i=1}^n H_i(s, B) \{ dN_i(s) - (D_i(s), Z_i) dB(s, \theta) \} + \int_0^t V_n(s-, \theta) \{ 1 + o_p(1) \} \sum_{i=1}^n \frac{\partial H_i(s, B)}{\partial B(s-, \theta)} dN_i(s) + o_p(1), \]
which by (45) yields
\[ V_n(t, \theta) = \frac{1}{\sqrt{n}} \int_0^t \sum_{i=1}^n H_i(s, B) \{ dN_i(s) - (D_i(s), Z_i) dB(s, \theta) \} + \int_0^t \sum_{i=1}^n \frac{\partial H_i(s, B)}{\partial G_{1,i}(s-)} (D_i(s-), Z_i) dN_i(s) \]
\[ + \int_0^t \sum_{i=1}^n \frac{\partial H_i(s, B)}{\partial G_{2,i}(s-)} \left[ \int_{s-}^s V_n(u, \theta) \{ 1 + o_p(1) \} d(D_i(u), Z_i) \right] dN_i(s) + o_p(1) \]
\[ = \frac{1}{\sqrt{n}} \int_0^t \sum_{i=1}^n H_i(s, B) \{ dN_i(s) - (D_i(s), Z_i) dB(s, \theta) \} + \int_0^t V_n(s-, \theta) \sum_{i=1}^n \left\{ \int_{s+}^t \frac{\partial H_i(u, B_D)}{\partial G_{2,i}(u-)} dN_i(u) \right\} (dD_i(s), dZ_i), \]
where the last equation follows by Fubini’s theorem. Together we have the Volterra-equation,
\[ V_n(t, \theta) = \frac{1}{\sqrt{n}} \int_0^t \sum_{i=1}^n H_i(s, B) \{ dN_i(s) - (D_i(s), Z_i) dB(s, \theta) \} \]
\[ + \int_0^t V_n(s-, \theta) \sum_{i=1}^n \left\{ \int_{s+}^t \frac{\partial H_i(u, B)}{\partial G_{1,i}(u-)} (D_i(u-), Z_i) dN_i(u) \right\} \left\{ \int_{s+}^t \frac{\partial H_i(u, B_D)}{\partial G_{2,i}(u-)} dN_i(u) \right\} (dD_i(s), dZ_i) \],
which admits a solution with explicit form given by
\[ V_n(t, \theta) = \frac{1}{\sqrt{n}} \int_0^t \mathcal{F}(s, t) \sum_{i=1}^n H_i(s, B) \{ dN_i(s) - (D_i(s), Z_i) dB(s, \theta) \} + o_p(1), \]
where
\[ \mathcal{F}(s, t) := \prod_{(s,t]} \left( 1 + \sum_{i=1}^n \left\{ \int_{s+}^t \frac{\partial H_i(u, B)}{\partial G_{1,i}(u-)} (D_i(u), Z_i) dN_i(u) + \left\{ \int_u^t \frac{\partial H_i(\cdot, B)}{\partial G_{2,i}(\cdot-)} dN_i(\cdot) \right\} d(D_i(u), Z_i) \right\} \right). \]
This leads to an i.i.d. representation

\[ V_n(t, \theta) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \epsilon_i^B(t) + o_p(1), \]

with the \( \epsilon_i^B(t) \) being zero-mean i.i.d. terms, defined as

\[ \epsilon_i^B(t) := \int_0^t \mathcal{F}(s,t) H_i(s,B) \{ dN_i(s) - D_i(s) dB_D(s) \}. \]

This, together with a Taylor expansion, gives

\[
\sqrt{n} \{ \hat{B}(t, \hat{\theta}) - B(t, \theta) \} = \sqrt{n} \{ \hat{B}(t, \theta) - B(t, \theta) \} + \sqrt{n} \{ \hat{B}(t, \theta) - B(t, \theta) \} \left. \frac{\partial B(t, \theta)}{\partial \theta} \right| \{ 1 + o_p(1) \} \sqrt{n} (\hat{\theta} - \theta) + o_p(1).
\]

Finally we have

\[
\sqrt{n} \{ \hat{B}(t, \hat{\theta}) - B(t, \theta) \} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \epsilon_i(t, \theta) + o_p(1),
\]

where

\[ \epsilon_i(t, \theta) := \epsilon_i^B(t) + \left. \frac{\partial B_Z(t, \theta)}{\partial \theta} \right| \epsilon_i^\theta. \]  

With this i.i.d. representation (58), similar arguments as in Lin et al. (2000), Martinussen et al. (2017) can be adopted to establish the convergence of \( V_n(t) \) in distribution to a Gaussian process. Also, (58) easily implies a variance estimate.

C Simulation Compatibility

We establish that our proposed data generating process in the simulation study ensures that Assumption 3 holds and is compatible with our model (1), where \( B_D(t) = 0.2t \) and \( B_Z(t) = 0.1t \).

To show that Assumption 3 holds, note that we first generate \( U \) from a normal distribution and \( Z \) from a random binomial distribution. Then we generate a shift variable \( W \) such that

\[ \mathbb{P}(W > t | Z, U) = \alpha(t; U)(2Z - 1) + \beta_0(t) + Z\beta_1(t), \]

where we should pick \( \alpha() \) and \( \beta() \) so \( \mathbb{P}(W > t | Z, U) \) is decreasing in \( t \) and between [0,1]. To make sure that the RHS indeed gives a valid distribution function for any \( Z \) and \( U \), we need

\[ \beta_0(0) = 1, \quad \alpha(0; U) = 0, \quad \beta_1(0) = 0, \]
and \( \alpha(t; U) + \beta_0(t) + \beta_1(t) \) and \(-\alpha(t; U) + \beta_0(t)\) nonnegative and decreasing. If choosing \( \beta_0(t) \) as a regular distribution function, then \( \alpha(t; U) \) and \( \beta_1(t) \) have to converge to 0 as \( t \to \infty \). Because \( D(t) = \mathbb{1}(W > t)Z + \mathbb{1}(W \leq t)(1 - Z) \), we have

\[
\mathbb{E}(D(t)|Z, U) = Z \mathbb{P}(W > t|Z, U) + (1 - Z)(1 - \mathbb{P}(W > t|Z, U)) = (2Z - 1) \mathbb{P}(W > t|Z, U) + 1 - Z = (2Z - 1)\beta(t; Z) + 1 - Z + \alpha(t; U).
\]

Therefore \( \alpha_Z(t; Z, L) = (2Z - 1)(\beta_0(t) + Z\beta_1(t)) + 1 - Z \) and \( \alpha_U(t; U) = \alpha(t; U) \).

To show that our data generating process is compatible with our model (1), where \( B_D(t) = 0.2t \) and \( B_Z(t) = 0.1t \), it suffices to show that,

\[
\frac{\mathbb{P}(\bar{T}(\bar{d}(m), \bar{0}, Z) > t|\bar{D}(m) = \bar{d}(m), Z, U, \bar{T} \geq m)}{\mathbb{P}(\bar{T}(\bar{d}(m - 1), \bar{0}, z = 0) > t|\bar{D}(m) = \bar{d}(m), Z = 0, U, \bar{T} \geq m)} = \exp\left\{ -0.2 \int_m^{t\wedge m + 1} d(m)dt - 0.1 \int_m^{t\wedge m + 1} Zdt \right\},
\]

which after integrating \( U \) out, yields (1). We work on the numerator of the LHS of (59) first,

\[
\mathbb{P}(\bar{T}(\bar{d}(m), \bar{0}, Z) > t|\bar{D}(m) = \bar{d}(m), Z, U, \bar{T} \geq m) = \frac{\mathbb{P}(\bar{T}(\bar{d}(m), \bar{0}, Z) > t|\bar{D}(m) = \bar{d}(m), Z, U)}{\mathbb{P}(\bar{T} > m|\bar{D}(m) = \bar{d}(m), Z, U)} = \frac{\mathbb{P}(\bar{T}(\bar{d}(m), 0, z > t|U)}{\mathbb{P}(\bar{T}(\bar{d}(m), 0, z > m|U)} = \exp\left\{ -0.1(t - m) - 0.2 \int_m^t d(s)ds - 0.1 \int_m^t Zds - 0.15U_2(t - m) \right\},
\]

where the second equation follows by consistency and unconfoundedness (conditional on \( U \)) guaranteed by our data generating process. Now we turn to the denominator of the LHS of (59),

\[
\mathbb{P}(\bar{T}(\bar{d}(m - 1), \bar{0}, z = 0) > t|\bar{D}(m) = \bar{d}(m), Z = 0, U, \bar{T} \geq m) = \frac{\mathbb{P}(\bar{T}(\bar{d}(m - 1), \bar{0}, Z = 0) > t|U)}{\mathbb{P}(\bar{T} > m|\bar{D}(m) = \bar{d}(m), Z = 0, U)} = \exp\left\{ -0.1(t - m) - 0.15U_2(t - m) \right\},
\]

now (59) is straightforward.