Estimating treatment effects with competing intercurrent events in randomized controlled trials

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Abstract

The analysis of randomized controlled trials is often complicated by intercurrent events (ICEs) – events that occur after treatment initiation and affect either the interpretation or existence of outcome measurements. Examples include treatment discontinuation or the use of additional medications. In two recent clinical trials for systemic lupus erythematosus with complications of ICEs, we classify the ICEs into two broad categories: treatment-related (e.g., treatment discontinuation due to adverse events or lack of efficacy) and treatment-unrelated (e.g., treatment discontinuation due to external factors such as pandemics or relocation). To define a clinically meaningful estimand, we adopt tailored strategies for each category of ICEs. For treatment-related ICEs, which are often informative about a patient's outcome, we use the *composite variable strategy* that assigns an outcome value indicative of treatment failure. For treatment-unrelated ICEs, we apply the *hypothetical strategy*, assuming their timing is conditionally independent of the outcome given treatment and baseline covariates, and hypothesizing a scenario in which such events do not occur. A central yet previously overlooked challenge is the presence of competing ICEs, where the first ICE censors all subsequent ones. Despite its ubiquity in practice, this issue has not been explicitly recognized or addressed in previous data analyses due to the lack of rigorous statistical methodology. In this paper, we propose a principled framework to formulate the estimand,

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establish its nonparametric identification and semiparametric estimation theory, and introduce weighting, outcome regression, and doubly robust estimators. We apply our methods to analyze the two systemic lupus erythematosus trials, demonstrating the robustness and practical utility of the proposed framework.

Keywords: Causal inference; Clinical trial; International Council for Harmonization; Post-treatment variable; Potential outcomes

1 Intercurrent events in randomized controlled trials

Randomized controlled trials (RCTs) are considered the gold standard for evaluating treatment efficacy, primarily because randomization supports assumption-lean inference of the treatment effect. However, after treatment initiation, various events, referred to as intercurrent events (ICEs), can arise, impacting the interpretation or availability of outcome measurements and posing significant challenges to the analysis of RCTs. Examples of ICEs include treatment discontinuation due to adverse events or lack of efficacy, patient relocation, and the use of additional medications. Carefully accounting for ICEs is essential to ensure the validity and reliability of the causal conclusions drawn from RCTs.

Recognizing the critical need for clearly defined estimands in the presence of ICEs, the International Council for Harmonization (ICH) issued the E9(R1) Addendum (ICH E9 (R1), 2019). This addendum introduces a structured estimand framework for clinical trials to obtain precisely defined treatment effects that align with the clinical questions of interest. It outlines strategies for addressing ICEs during the formulation of the clinical question and emphasizes that careful specification of the treatment, population, and outcome variable often addresses many of the ICEs raised in discussions between sponsors and regulators. Since its release, the ICH E9(R1) Addendum has been widely discussed, increasingly adopted in clinical drug development, and has sparked substantial interest in statistical research (Qu et al., 2021; Kang et al., 2022; Ionan et al., 2023; Han and Zhou, 2023; Olarte Parra et al., 2025).

A widely accepted strategy is the *treatment policy strategy* (ICH E9 (R1), 2019), which includes all participants in their originally assigned groups and uses the observed outcome values, regardless of whether or not an ICE occurs. This approach aligns with the intention-to-treat principle and reflects the effect of a treatment policy in real clinical settings. However, it cannot address ICEs that are terminal events, such as death, because such events preclude the existence of the outcome

variable.

The *composite variable strategy* is an alternative approach that is well-suited for handling ICEs that are informative of the patient's outcome such as the terminal events. This strategy incorporates the occurrence of ICEs directly into the outcome definition. Specifically, it defines a composite outcome: if no ICE occurs, the outcome of interest is used as observed; if an ICE occurs, a pre-specified, clinically meaningful value—typically indicating treatment failure—is assigned. This strategy is widely used in practice across various types of outcomes, including binary outcomes (e.g., the non-responder imputation approach), ordinal or continuous outcomes (e.g., Rosenbaum, 2006), and time-to-event outcomes (e.g., progression-free survival).

In addition to the treatment policy and composite variable strategies, ICH E9 (R1) (2019) outlines three additional strategies for handling ICEs. The *hypothetical strategy* evaluates treatment effects under a hypothetical scenario in which the ICE would not occur. The *while-on-treatment* and *principal stratification strategies* are also described but are less commonly used in current practice due to their reliance on strong assumptions and the potential to introduce bias in treatment comparisons. ICH E9 (R1) (2019) recommends using different strategies based on the specific type of ICEs involved. While some studies have explored the use of multiple strategies (Lipkovich et al., 2020; Qu et al., 2021), none have rigorously examined how to combine different strategies, nor have they rigorously addressed the potential pitfalls of doing so without careful consideration. Moreover, the challenges posed by competing ICEs remain unrecognized.

1.1 Two phase-3 trials in systemic lupus erythematosus

To rigorously examine the challenges posed by ICEs in clinical trials, we analyze data from two recent randomized studies for systemic lupus erythematosus (Morand et al., 2023; Petri et al., 2023), in which participants were randomly assigned to either the baricitinib treatment group or the placebo control group. These twin trials were designed to provide substantiated evidence on the causal treatment effect of baricitinib versus placebo.

The primary outcome is a response index measured at 52 weeks after treatment initiation. Ideally, this outcome would be compared directly between the two treatment groups at week 52. However, 429 out of 1,535 patients (27.95%) experienced ICEs during the follow-up period, resulting in unobserved outcome data. Figure 1 shows the types and proportions of these ICEs. During the 52-week period,

various ICEs occurred: some patients discontinued treatment due to adverse events or lack of efficacy; others discontinued treatment due to study withdrawal for unspecified reasons or were lost to follow-up; and some were excluded from the study due to protocol deviations. We revisit this example in greater detail in Section 5.
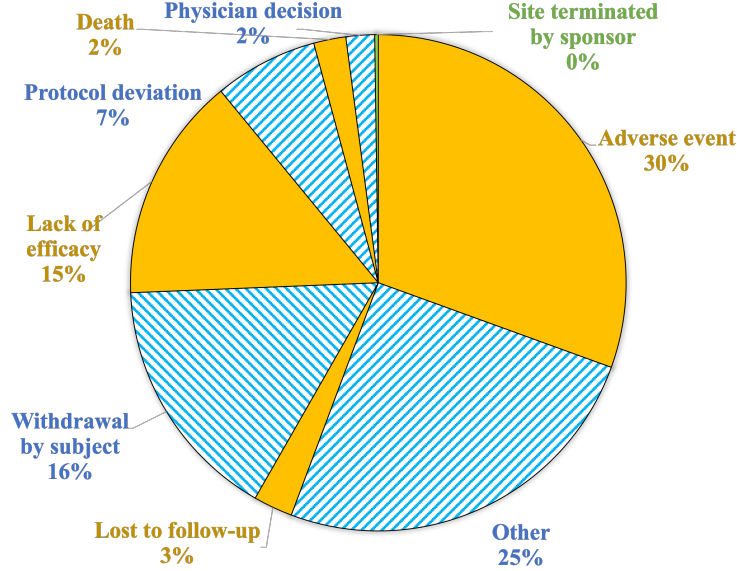

Figure 1: Pie chart showing the ICE types and proportions. The yellow solid charts represent treatment-related ICEs, the green solid chart represents a treatment-unrelated ICE, and the blue striped charts represent a mix of both types.

1.2   Our proposal and contribution

We propose to classify ICEs into two broad types: (1) treatment-unrelated ICEs, such as treatment discontinuation due to relocation or COVID-19 lockdown, which are assumed to be independent of treatment efficacy conditional on the observed covariates; and (2) treatment-related ICEs, such as treatment discontinuation due to adverse events or lack of efficacy, use of rescue medication, and terminating events such as death, which are often informative about a patient's outcome.

In our application studies, the two types of ICEs were classified based on a manual review of the detailed comments collected at the clinical sites. Figure 1 summarizes the main categories and illustrates our classification scheme: yellow solid charts represent treatment-related ICEs, the green solid chart represents a treatment-unrelated ICE, and the blue striped charts represent a mix of both types. For instance, some patients withdrew from the study due to external factors such as relocation or the COVID-19 pandemic, which were classified as treatment-unrelated. Others withdrew due to
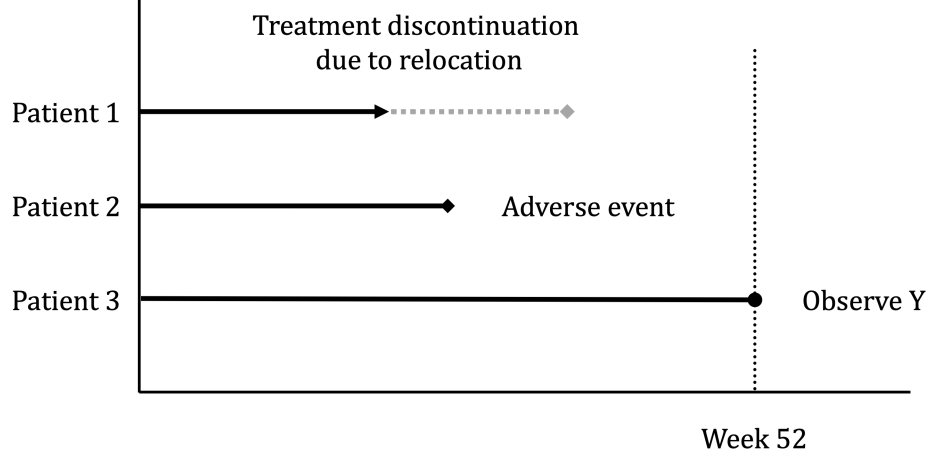
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Figure 2: Illustration of three representative scenarios of intercurrent events in the immunology trial. The primary outcome is measured at week 52, and the solid lines indicate the observed follow-up period for each patient. Patient 1 experienced a treatment-unrelated ICE (represented by an arrow), Patient 2 experienced a treatment-related ICE (represented by a diamond), and Patient 3 had no ICE before week 52. This figure highlights the issue of competing ICEs: for instance, had Patient 1 not discontinued early and remained on treatment (illustrated by the gray dashed line), they might have experienced a treatment-related ICE later in the follow-up period.

concerns about potential side effects, which were considered treatment-related. When the reason for withdrawal was not clearly stated, we adopted a conservative approach and classified the ICE as treatment-related. Both types of ICEs may occur during the follow-up period. Figure 2 depicts the timeline and three representative scenarios from our motivating example. Before week 52, patient 1 withdrew from the study due to relocation, which is arguably unrelated to treatment. Patient 2 dropped out due to an adverse event, reflecting a treatment-related ICE. Patient 3 completed the study through week 52, at which point the primary outcome was measured.

Both types of ICEs lead to unmeasured primary outcomes at the pre-specified landmark time because the outcome cannot be observed or may not even be well-defined when a treatment-related ICE occurs. To ensure the estimand is clinically interpretable and relevant, we apply different strategies tailored to the nature of the ICE. For ICEs that are plausibly unrelated to treatment (e.g., treatment discontinuation due to relocation or administrative withdrawal), we apply the *hypothetical strategy*, which imagines a scenario where the ICE did not occur. This enables estimation of the treatment effect as if the patient had remained on treatment and in the study as planned, under the assumption that the ICE time is conditionally independent of the outcome given treatment and baseline covariates. This assumption is reasonable in settings where the ICE arises from external

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or administrative factors that are not influenced by post-randomization conditions. For example, if a patient relocates for personal reasons unrelated to their health status or treatment response, then, conditional on baseline characteristics and assigned treatment, the occurrence of this ICE can be viewed as independent of the patient's outcome. In contrast, for treatment-related ICEs (e.g., treatment discontinuation due to adverse events or lack of efficacy), we apply the *composite variable strategy*, treating the ICE itself as an indication of treatment failure, as such events signify that the patient is unable to continue treatment. A formal definition and discussion of this strategy are provided in Section 3. Combining the two strategies enhances the interpretability of the estimand and ensures it better reflects clinically relevant questions, as no single strategy can adequately address both types of ICEs. Specifically, it would be inappropriate to classify a patient as a non-responder if they discontinue treatment due to relocation, and it is of limited clinical relevance to consider a hypothetical scenario in which adverse events do not occur. This approach is consistent with regulatory guidance, which recommends applying different strategies depending on the type of ICE involved (ICH E9 (R1), 2019; Kang et al., 2022).

However, a central yet previously overlooked challenge is the presence of *competing ICEs*, where the first ICE censors all subsequent ones. For example, if a patient discontinues treatment due to relocation, as illustrated by patient 1 in Figure 2, we only observe that no treatment-related ICE occurred before the discontinuation. However, it remains unknown whether an adverse event would have occurred before the final outcome measurement in the hypothetical scenario in which the patient had not relocated and had continued treatment as planned. Although such competing ICEs are ubiquitous in practice, this issue has not, to our knowledge, been explicitly recognized or addressed in prior methodological work.

The central thesis of this paper is to address the challenge of competing ICEs. We begin by developing a principled framework that clearly defines the estimand and establishes its nonparametric identification. Specifically, we derive two identification formulas, each relying on a different set of nuisance parameters. Building on these results, we propose two basic estimators corresponding to the two identification strategies. We then introduce an augmented estimator that combines the two, achieving double robustness. To further enhance both robustness and efficiency, we derive the efficient influence function (EIF) and construct an EIF-based estimator that attains the semiparametric efficiency bound under appropriate conditions. We apply our methods to the two systemic

lupus erythematosus trials, both partially impacted by the COVID-19 pandemic, demonstrating the robustness and practical utility of the proposed framework.

1.3 Organization and notation

The remainder of the paper is organized as follows. In Section 2, we present a motivating example, introduce the basic setup of our research question, define the causal parameter of interest, and highlight the identification challenge. In Section 3, we state the key identification assumptions, establish the nonparametric identification of the causal parameter, and construct three estimators. In Section 4, we derive the EIF, propose an estimator that is both doubly robust and asymptotically efficient, and examine its asymptotic properties. In Section 5, we apply the methods to re-analyze the two systemic lupus erythematosus trials. Finally, in Section 6, we conclude with a discussion of two directions for future research. The supplementary material includes a simulation study and all proofs. We also provide publicly available R code implementing all four proposed estimators.

We use the following notation. Let $\|r\|_2 = \{\int r(o)^2 \mathrm{d}P(o)\}^{1/2}$ denote the $L_2(P)$ norm where $P(\cdot)$ denotes the distribution of the observed data $O = o$. For the survival functions, let $\|r\|_2 = \{\iint r(t,o)^2 \mathrm{d}P(o)\mathrm{d}t\}^{1/2}$ denote the $L_2(P)$ norm. We write $b_n = O_P(a_n)$ if b_n/a_n is bounded in probability and $b_n = o_P(a_n)$ if b_n/a_n converges to 0 in probability.

2 Setup and estimand

2.1 Setup

Let A denote the binary treatment indicator, where $A = 1$ corresponds to assignment to the treatment group and $A = 0$ to the control group. The primary outcome, denoted by Y, is measured at a pre-specified time point k. In our motivating example, Y represents the response index, and k corresponds to 52 weeks. We adopt the potential outcomes framework, in which $Y(a)$ denotes the potential outcome under treatment assignment $A = a$, for $a = 0, 1$. The observed outcome is then given by $Y = Y(A) = AY(1) + (1 - A)Y(0)$.

As discussed in Section 1, two types of ICEs may occur after treatment initiation: treatment-unrelated ICEs and treatment-related ICEs. To formally define these, let C and T denote the time to a treatment-unrelated ICE and the time to a treatment-related ICE, respectively. Since both are post-treatment variables, we use $C(a)$ and $T(a)$ to denote their potential values under

treatment assignment $A = a$, for $a = 0, 1$. The observed times are then given by $C = C(A) = AC(1) + (1 - A)C(0)$ and $T = T(A) = AT(1) + (1 - A)T(0)$.

2.2 Causal estimand and challenges in identification

To address treatment-related ICEs, we define a composite potential outcome as

$$Y^{\mathrm{cp}}(a) = Y(a)1\{T(a) > k\}$$

for $a = 0, 1$, where the superscript denotes "composite". This construction defines the outcome as zero (i.e., failure) if a treatment-related ICE occurs before the outcome is measured. We then define our causal estimand as the mean contrast:

$$\tau = E\{Y^{\mathrm{cp}}(1) - Y^{\mathrm{cp}}(0)\} = E[Y(1)1\{T(1) > k\}] - E[Y(0)1\{T(0) > k\}]. \tag{1}$$

This is the estimand under the *composite variable strategy*. It is widely used for binary outcomes to represent treatment success or failure, where treatment-related ICEs such as adverse events or lack of efficacy are treated as failures (ICH E9 (R1), 2019). In our motivating example, $Y(a)$ indicates whether a patient would be a responder at week 52 under treatment assignment $A = a$, had no ICE occurred. For patients who experience a treatment-related ICE before week 52, $Y(a)$ is unobserved. Under the composite variable strategy, these patients are defined as non-responders.

The composite variable approach extends beyond binary outcomes and is applicable in settings where treatment failure can be defined using a clinically meaningful threshold. Specifically, for outcomes such as quality of life, chronic pain, physical functioning, and cognitive performance that are typically measured on an ordinal or continuous scale, if a predefined value v may be used to indicate treatment failure, then a composite outcome under treatment assignment $A = a$ can be constructed as $Y(a)1\{T(a) > k\} + v1\{T(a) \leq k\}$, where the outcome retains its actual value if no treatment-related ICE occurs before time k, and takes the failure value v otherwise. The corresponding causal estimand can then be defined as in (1), with $Y(a)$ replaced by $Y(a) - v$ for $a = 0, 1$. Rosenbaum (2006) discussed a similar causal parameter in settings where the ICE is death and the outcome of interest is a measure of quality of life assessed after a fixed period.

Identifying τ in the presence of both types of ICEs presents a key methodological challenge.

For clarity, in the remainder of this subsection, we use treatment discontinuation due to relocation and adverse events to represent treatment-unrelated and treatment-related ICEs, respectively. The causal estimand τ defined in (1) is based on the composite potential outcome $Y^{\mathrm{cp}}(a)$, which takes the value 0 if an adverse event occurs before the outcome measurement, i.e., when $T(a) < k$. If adverse event were the only type of ICE, and treatment is randomized, τ could be identified from observed data using the difference in means of the composite outcomes: $\tau = E\{Y1(T > k) \mid A = 1\} - E\{Y1(T > k) \mid A = 0\}$. However, this formula is infeasible in the presence of treatment-unrelated ICEs, which may occur before treatment-related ICEs and thus censor both $T(a)$ and Y. As illustrated in Figure 2, patient 1 discontinued due to relocation, which censored both the occurrence of a potential adverse event and the outcome, resulting in an unobserved composite outcome $Y1(T > k)$. Therefore, for patients who experience treatment-unrelated ICEs, the problem cannot be treated as standard censoring, and one cannot naïvely impute the outcome Y under a hypothetical scenario where the treatment-unrelated ICE did not occur. This is because such patients may still have experienced a treatment-related ICE had they not discontinued due to relocation. In other words, a valid identification strategy must recover the expected value of the composite outcome $Y1(T > k)$, rather than the outcome Y alone.

Table 1 summarizes the observed ICE types and corresponding composite outcomes, highlighting that competing ICEs complicate the identification of τ. When no ICE occurs, the outcome Y is observed and equals the composite outcome since $T > k$. When an adverse event is observed, the composite outcome is, by definition, 0. However, when a patient discontinues treatment due to relocation, both the outcome Y and the time to the adverse event T are unobserved, and so is the composite outcome. We address this challenge and present formal identification results in the following section.

3 Nonparametric identification and basic estimators

3.1 Assumptions

We assume that the joint distribution of $\{X_i, A_i, T_i(1), T_i(0), C_i(1), C_i(0), Y_i(1), Y_i(0)\}$ for patient i is independently and identically distributed from a superpopulation. For notational simplicity, we omit the subscript i when there is no confusion.

We begin by stating the following assumption on treatment assignment.

Table 1: Summary of the observed ICE types and outcome. C is the time to treatment discontinuation due to relocation, T is the time to adverse event, Y is the outcome of interest, and k is the pre-specified time point when the measurement of Y is taken. A question mark "?" indicates that the corresponding value is unobserved.

observed ICE type	(T, C, k)-relationship	Y	$1(T > k)$	composite outcome Y^{cp}
no any type of ICE	$C \wedge T > k$	Y	1	Y
adverse event	$C \wedge k > T$	?	0	0
treatment discontinuation due to relocation	$T \wedge k > C$	?	?	?

ASSUMPTION 1 (TREATMENT ASSIGNMENT) *We assume the following conditional independence and overlap conditions:*

(a) $A \perp\!\!\!\perp \{Y(a), T(a), C(a)\} \mid X$ *for* $a = 0, 1$.

(b) *For some constant* $\eta \in (0, 0.5)$, $\eta < e(X) < 1 - \eta$ *with probability 1, where* $e(X) = \mathrm{pr}(A = 1 \mid X)$ *denotes the propensity score (Rosenbaum and Rubin, 1983).*

Assumption 1 holds in RCTs by design, allowing our results to apply directly to settings such as our motivating example. However, our formulation is more general and can also accommodate cases where treatment assignment is not completely randomized, such as in stratified randomized experiments and observational studies.

Under Assumption 1, the causal estimand τ can be expressed as:

$$
\begin{aligned}
\tau &= E[E\{Y1(T > k) \mid A = 1, X\} - E\{Y1(T > k) \mid A = 0, X\}] \\
&= E\left\{ \frac{AY1(T > k)}{e(X)} - \frac{(1 - A)Y1(T > k)}{1 - e(X)} \right\},
\end{aligned}
$$

which correspond to the standard outcome regression and inverse probability weighting identification formulas, respectively, when treating the composite potential outcome $Y^{\mathrm{cp}}(a) = Y(a)1\{T(a) > k\}$ as the "new" outcome of interest. However, as discussed in Section 2.2, these expressions no longer serve as feasible identification formulas in the presence of competing treatment-unrelated ICEs. This is because $Y1(T > k)$ is not fully observed if a treatment-unrelated ICE occurs.

To address this challenge, we introduce additional assumptions regarding treatment-unrelated ICEs. Specifically, we assume that the potential time of a treatment-unrelated ICE under treatment

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a is conditionally independent of the potential outcomes and the potential time to treatment-related ICEs, given baseline covariates. This assumption is analogous to the censoring-at-random assumption in survival analysis when treating treatment-unrelated ICEs as censoring events (Robins et al., 1994; Tsiatis, 2006). Additionally, we require that the probability of no occurrence of treatment-unrelated ICE by time k, given observed covariates, is strictly positive. These conditions are summarized in the following assumption.

ASSUMPTION 2 (TREATMENT-UNRELATED ICE) *We assume the following conditional independence and positivity conditions for the time of treatment-unrelated ICE:*

(a) $C(a) \perp\!\!\!\perp \{Y(a), T(a)\} \mid X$ *for* $a = 0, 1$.

(b) *For some constant* $\eta_C > 0$, $\mathrm{pr}\{C(a) > k \mid X\} > \eta_C$ *with probability 1.*

In our motivating example, Assumption 2(a) states that the time to a treatment-unrelated ICE, such as treatment discontinuation due to relocation, is independent of both the potential outcome (i.e., whether a patient would be a responder at week 52) and the time to a treatment-related ICE (e.g., an adverse event), conditional on observed baseline covariates. In other words, after accounting for baseline covariates such as geographic region, baseline corticosteroid use, and the physician's global assessment score, the decision to discontinue treatment due to relocation is assumed to be unrelated to the patient's potential outcomes or potential timing of adverse events. Assumption 2(b) requires that every patient has a strictly positive probability of not experiencing a treatment-unrelated ICE before time k, given their covariates. This standard positivity condition rules out deterministic treatment-unrelated ICE happening in any subpopulation and is reasonable in our application.

3.2 Two identification formulas

Using the composite variable strategy to handle treatment-related ICEs, recall that we define the causal estimand as in (1). Under Assumptions 1 and 2, we show that the estimand τ is nonparametrically identifiable and present two identification formulas in the following theorem.

THEOREM 1 (NONPARAMETRIC IDENTIFICATION OF τ) *Under Assumptions 1 and 2, τ is nonpara-*

metrically identified by two distinct formulas. First,

$$\tau \;=\; E\left\{\mu_1(X)S_1(k\mid X)-\mu_0(X)S_0(k\mid X)\right\}, \qquad (2)$$

where for $a=0,1$, $\mu_a(X)=E(Y\mid T\wedge C>k,X,A=a)$ is the conditional mean of observed outcome among those with no ICE and $A=a$, and $S_a(t\mid X)=\mathrm{pr}(T>t\mid X,A=a)$ is the conditional survival function of treatment-related ICE in treatment arm a. Second,

$$\tau \;=\; E\left[\frac{AY\mathbf{1}(T\wedge C>k)}{e(X)G_1(k\mid X)}-\frac{(1-A)Y\mathbf{1}(T\wedge C>k)}{\{1-e(X)\}\,G_0(k\mid X)}\right], \qquad (3)$$

where $e(X)=\mathrm{pr}(A=1\mid X)$ is the propensity score and for $a=0,1$, $G_a(t\mid X)=\mathrm{pr}(C>t\mid X,A=a)$ is the conditional survival function of treatment-unrelated ICE in treatment arm a.

The first identification formula (2) expresses τ using a standard outcome regression approach. It decomposes the conditional expectation of the composite outcome given covariates and treatment as $E\{YI(T>k)\mid X,A\}=E(Y\mid T>k,X,A)P(T>k\mid X,A)=E(Y\mid T\wedge C>k,X,A)P(T>k\mid X,A)$. This formulation models the conditional mean outcome Y among individuals who do not have any ICE by time k, and weights it by the probability of not experiencing a treatment-related ICE by that time. The second identification formula (3) provides an alternative identification strategy based on inverse probability weighting. It identifies τ by reweighting observed outcomes among individuals who remain free of ICEs up to time k, separately within each treatment arm. The weights adjust for the different probability of observing the composite outcome and consist of two components: $e(X)$, which accounts for differences in treatment assignment probabilities, and $G_a(k\mid X)$, which adjusts for the probability of remaining free of treatment-unrelated ICEs up to time k within each treatment group. Effectively, individuals with a lower probability of being observed are up-weighted, while those with a higher probability are down-weighted, ensuring an unbiased estimate of the treatment effect.

Both equations (2) and (3) are valid identification formulas, as the nuisance parameters involved are either functions of observed data or identifiable from observed data. Specifically, the propensity score $e(X)$ and the conditional outcome model $\mu_a(X)$ are functions of observed data. Although the survival functions for both types of ICEs, $S_a(t\mid X)$ for treatment-related ICEs and $G_a(t\mid X)$ for treatment-unrelated ICEs, are not direct functions of the observed data, they are identifiable under

standard results in survival analysis with censoring at random (Robins and Rotnitzky, 1992; Robins and Finkelstein, 2000; Ebrahimi et al., 2003). For example, $S_1(t \mid X) = \mathrm{pr}(T > t \mid X, A = 1)$ for $t \leq k$ can be estimated using data from the treatment group by viewing $T \wedge C \wedge k$ as the observed event time and using $1(C \wedge k \geq T)$ as the event indicator for the treatment-related ICE. Estimation can then proceed using parametric or semiparametric methods, such as the Cox proportional hazards model (Cox, 1972), or more flexible approaches (Wolock et al., 2024). A similar approach can be used to estimate $G_1(t \mid X)$ by switching the roles of T and C. The corresponding functions $S_0(t \mid X)$ and $G_0(t \mid X)$ can be estimated in the same way using data from the control group.

3.3 Two basic estimators

The identification formulas (2) and (3) in Theorem 1 motivate two basic estimators, each relying on estimates of the corresponding nuisance functions. Let $\hat{S}_a(t \mid X)$ and $\hat{G}_a(t \mid X)$ denote the fitted survival models for treatment-related and treatment-unrelated ICEs, respectively, for $t \leq k$ and $a = 0, 1$. Let $\hat{\mu}_a(X)$ be the fitted outcome regression model for each treatment arm, and $\hat{e}(X)$ be the fitted propensity score model. By substituting these fitted values into the identification formulas and taking empirical analogs, we obtain the following two estimators:

$$
\begin{aligned}
\hat{\tau}^{\mathrm{out}} &= n^{-1} \sum_{i=1}^{n} \hat{\mu}_1(X_i)\hat{S}_1(k \mid X_i) - n^{-1} \sum_{i=1}^{n} \hat{\mu}_0(X_i)\hat{S}_0(k \mid X_i), \\
\hat{\tau}^{\mathrm{ipw}} &= n^{-1} \sum_{i=1}^{n} \frac{A_i Y_i 1(T_i \wedge C_i > k)}{\hat{e}(X_i)\hat{G}_1(k \mid X_i)} - n^{-1} \sum_{i=1}^{n} \frac{(1 - A_i)Y_i 1(T_i \wedge C_i > k)}{\{1 - \hat{e}(X_i)\}\hat{G}_0(k \mid X_i)}.
\end{aligned}
$$

The outcome regression estimator $\hat{\tau}^{\mathrm{out}}$ is consistent if both $\hat{\mu}_a(X)$ and $\hat{S}_a(k \mid X)$ are consistently estimated. The inverse probability weighting estimator $\hat{\tau}^{\mathrm{ipw}}$ is consistent if both $\hat{e}(X)$ and $\hat{G}_a(k \mid X)$ are consistently estimated.

3.4 An augmented estimator

By combining the two identification formulas (2) and (3), we derive the following augmented identification formula:

$$
\begin{aligned}
\tau = {} & E \left\{ \frac{AY 1(T \wedge C > k)}{e(X)G_1(k \mid X)} - \frac{A - e(X)}{e(X)}\mu_1(X)S_1(k \mid X) \right\} \\
& - E \left[\frac{(1 - A)Y 1(T \wedge C > k)}{\{1 - e(X)\}G_0(k \mid X)} - \frac{e(X) - A}{1 - e(X)}\mu_0(X)S_0(k \mid X) \right].
\end{aligned} \tag{4}
$$

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Equation (4) can be interpreted both as a modified form of the outcome regression identification formula (2), and as an augmented form of the weighting identification formula in (3). Under the true model at the population level, the correction terms have mean 0, and thus (4) holds by construction. However, it becomes meaningful in the presence of possible model misspecification, where the augmentation plays a crucial role in improving robustness.

Based on (4), we construct an estimator that augments the weighting estimator $\hat{\tau}^{\mathrm{ipw}}$ using the estimated outcome models,

$$
\hat{\tau}^{\mathrm{aug}} = \hat{\tau}^{\mathrm{ipw}} - n^{-1} \sum_{i=1}^{n} \left\{ \frac{A_i - \hat{e}(X_i)}{\hat{e}(X_i)} \hat{\mu}_1(X_i) \hat{S}_1(k \mid X_i) + \frac{A_i - \hat{e}(X_i)}{1 - \hat{e}(X_i)} \hat{\mu}_0(X_i) \hat{S}_0(k \mid X_i) \right\}.
$$

It has a similar mathematical form to the classic augmented inverse probability weighting estimator for the average treatment effect (Bang and Robins, 2005). We provide the properties of $\hat{\tau}^{\mathrm{aug}}$ in the following Proposition 1.

PROPOSITION 1 (DOUBLE ROBUSTNESS OF $\hat{\tau}^{\mathrm{aug}}$) *Suppose Assumptions 1 and 2 hold, and assume that $G_a(k \mid X)$ is correctly specified for $a = 0, 1$. $\hat{\tau}^{\mathrm{aug}}$ is a consistent estimator for τ if either $e(X)$ is correct, or both $\mu_a(X)$ and $S_a(k \mid X)$ are correct for $a = 0, 1$.*

Proposition 1 shows that the consistency of $\hat{\tau}^{\mathrm{aug}}$ depends on correctly specifying $G_a(k \mid X)$ for $a = 0, 1$, while it remains robust to misspecification of the propensity score $e(X)$. To build intuition, from the perspective of semiparametric efficiency theory, Equation (4) can be viewed as a projection of the weighting identification formula (3) onto the nuisance tangent space of the propensity score model $A \mid X$. However, because it is not further projected onto the nuisance tangent space of the $G_a(k \mid X)$ model, the resulting estimator does not retain robustness to misspecification of $G_a(k \mid X)$. We will further address the issue in Section 4, where we introduce an alternative estimator that is robust to the misspecification of both models.

The augmented estimator $\hat{\tau}^{\mathrm{aug}}$ dominates the weighting estimator $\hat{\tau}^{\mathrm{ipw}}$ in terms of robustness. The consistency of $\hat{\tau}^{\mathrm{aug}}$ is contingent on less restrictive requirements on nuisance parameter estimation in the sense that $\hat{\tau}^{\mathrm{aug}}$ is consistent whenever $\hat{\tau}^{\mathrm{ipw}}$ is. Consistency of $\hat{\tau}^{\mathrm{aug}}$ requires the correct specification of the survival function for treatment-unrelated ICE $G_a(k \mid X)$ for $a = 0, 1$. Given that $G_a(k \mid X)$ is correctly modeled, $\hat{\tau}^{\mathrm{aug}}$ is doubly robust because it is consistent if either the propensity score model is correct, or the outcome regression and the survival model for treatment-related ICEs

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are both correct. There is no clear dominance between $\hat{\tau}^{\mathrm{aug}}$ and $\hat{\tau}^{\mathrm{out}}$ as they require consistent estimation of different sets of nuisance parameters. For all three estimators $\hat{\tau}^{\mathrm{out}}$, $\hat{\tau}^{\mathrm{ipw}}$, and $\hat{\tau}^{\mathrm{aug}}$, we can construct variance estimators using nonparametric bootstrap.

4 A semiparametrically efficient and doubly robust estimator

The augmented weighting estimator $\hat{\tau}^{\mathrm{aug}}$ improves robustness of $\hat{\tau}^{\mathrm{ipw}}$. However, it is not robust to the misspecification of the survival function for treatment-unrelated ICE, nor does it achieve the semiparametric efficiency bound. In this section, we show that $\hat{\tau}^{\mathrm{aug}}$ can be further improved. We derive the semiparametric efficient influence function (EIF) for τ to learn the best asymptotic efficiency a consistent estimator of τ can achieve and propose an asymptotically efficient and doubly robust estimator based on the EIF.

We first describe the full and observed data structures in our setting and introduce some additional notation. Ideally, we want to observe the full data $(X, Y^{\mathrm{cp}}(1), Y^{\mathrm{cp}}(0))$. The missingness of the full data comes from two strings. First, for a given treatment arm $a = 0, 1$, the treatment-unrelated ICE time $C(a)$ censors the full data because $Y^{\mathrm{cp}}(a)$ is only observable if $C(a) \geq \{T(a) \wedge k\}$. Within each treatment group, we do not observe the full data due to censoring and only observe

$$(\Delta(a) = 1\{C(a) \geq T(a) \wedge k\}, \tilde{T}(a) = C(a) \wedge T(a) \wedge k, \Delta(a)Y^{\mathrm{cp}}(a)).$$

Second, the treatment assignment generates another level of missingness, because, for each observation, we never simultaneously observe both composite potential outcomes $\{Y^{\mathrm{cp}}(1), Y^{\mathrm{cp}}(0)\}$ even without censoring. Therefore, the observed data is

$$O = (A, \Delta = \Delta(A), \tilde{T} = \tilde{T}(A), \Delta Y^{\mathrm{cp}} = \Delta(A)Y^{\mathrm{cp}}(A)).$$

4.1 EIF and EIF-based estimator

In the following theorem, we provide the EIF for τ.

THEOREM 2 (EIF FOR τ) *Under the nonparametric model, the EIF for μ_1 is*

$$D_1(O) = \frac{A}{e(X)}\left\{\frac{Y 1(T \wedge C > k)}{G_1(k \mid X)} + \mu_1(X)S_1(k \mid X)\int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1}(t)}{S_1(t \mid X)G_1(t \mid X)}\right\}$$

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$$-\frac{A - e(X)}{e(X)}\mu_1(X)S_1(k \mid X) - \mu_1, \tag{5}$$

the EIF for μ_0 is

$$
\begin{aligned}
D_0(O) &= \frac{1-A}{1-e(X)}\left\{\frac{Y1(T \wedge C > k)}{G_0(k \mid X)} + \mu_0(X)S_0(k \mid X)\int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_0}(t)}{S_0(t \mid X)G_0(t \mid X)}\right\} \\
&\quad - \frac{e(X) - A}{1 - e(X)}\mu_0(X)S_0(k \mid X) - \mu_0,
\end{aligned}
\tag{6}
$$

and thus, the EIF for τ is $D_\tau(O) = D_1(O) - D_0(O)$, where $\mathrm{d}M_{G_a}(t) = 1(C \in \mathrm{d}t, \Delta = 0) - 1(\tilde{T} \geq t)\mathrm{d}\Lambda_a(t \mid X)$ with $\Lambda_a(t \mid X)$ denoting the conditional cumulative hazard function for the treatment-unrelated ICE C in the treatment group $A = a$ for $a = 0, 1$.

The $M_{G_a}(t)$ in the EIF is the martingale constructed from the censoring counting process. Intuitively, $1(C \in \mathrm{d}t, \Delta = 0)$ is the actual observed increment in the censoring counting process at time t, which records whether a censoring event has occurred, while $1(\tilde{T} \geq t)\mathrm{d}\Lambda_a(t \mid X)$ represents the expected increment in the counting process, given the history up to time t. The martingale $M_{G_a}(t)$ captures the difference between the actual observed events and their expected occurrences. The EIF implies another identification formula for τ by the property that $E\{D_\tau(O)\} = 0$. Rearranging terms, we have

$$
\begin{aligned}
\tau &= E\left\{\frac{AY1(T \wedge C > k)}{e(X)G_1(k \mid X)} - \frac{A - e(X)}{e(X)}\mu_1(X)S_1(k \mid X)\right\} \\
&\quad - E\left[\frac{(1-A)Y1(T \wedge C > k)}{\{1 - e(X)\}G_0(k \mid X)} - \frac{e(X) - A}{1 - e(X)}\mu_0(X)S_0(k \mid X)\right] \\
&\quad + E\left[\frac{A}{e(X)}\mu_1(X)S_1(k \mid X)\int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1}(t)}{S_1(t \mid X)G_1(t \mid X)}\right] \\
&\quad - E\left[\frac{1-A}{1-e(X)}\mu_0(X)S_0(k \mid X)\int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_0}(t)}{S_0(t \mid X)G_0(t \mid X)}\right],
\end{aligned}
\tag{7}
$$

where the first two lines are the same as in the augmented weighting identification formula (4). Intuitively, we further augment (4) by the last two terms in (7) to achieve robustness to misspecification of the survival function for treatment-unrelated ICE. These augmentation terms are zero at the population level under true $G_a(t \mid X)$. However, their empirical counterparts may deviate significantly from zero, providing diagnostic insight into possible misspecification of $G_a(t \mid X)$.

The EIFs in Theorem 2 motivate the following estimator for τ,

$$\hat{\tau}^{\text{eif}} = \hat{\tau}^{\text{aug}} + n^{-1} \sum_{i=1}^{n} \frac{A_i}{\hat{e}(X_i)} \hat{\mu}_1(X_i) \hat{S}_1(k \mid X_i) \int_0^{\tilde{T}_i} \frac{dM_{\hat{G}_1}(t)}{\hat{S}_1(t \mid X_i) \hat{G}_1(t \mid X_i)}$$
$$- n^{-1} \sum_{i=1}^{n} \frac{1 - A_i}{1 - \hat{e}(X_i)} \hat{\mu}_0(X_i) \hat{S}_0(k \mid X_i) \int_0^{\tilde{T}_i} \frac{dM_{\hat{G}_0}(t)}{\hat{S}_0(t \mid X_i) \hat{G}_0(t \mid X_i)}.$$

To gain insights, consider the first augmentation term in $\hat{\tau}^{\text{eif}}$. Since the observed time points are discrete, the integral for observation i can be estimated as follows:

$$\int_0^{\tilde{T}_i} \frac{dM_{\hat{G}_1}(t)}{\hat{S}_1(t \mid X_i) \hat{G}_1(t \mid X_i)} = \sum_{t \leq \tilde{T}_i} \frac{1(\Delta_i = 0, C_i = t) - \hat{\lambda}_1(t \mid X_i)}{\hat{S}_1(t \mid X_i) \hat{G}_1(t \mid X_i)}$$
$$= - \sum_{t \leq \tilde{T}_i} \frac{\hat{\lambda}_1(t \mid X_i)}{\hat{S}_1(t \mid X_i) \hat{G}_1(t \mid X_i)} + \frac{1(\Delta_i = 0)}{\hat{S}_1(\tilde{T}_i \mid X_i) \hat{G}_1(\tilde{T}_i \mid X_i)}, \quad (8)$$

where $\hat{\lambda}_1(t \mid X_i)$ denotes the estimated conditional hazard function for the treatment-unrelated ICE at time t given covariates X_i. In (8), the first term is a sum of the ratio $-\hat{\lambda}_1(t \mid X_i)/\{\hat{S}_1(t \mid X_i) \hat{G}_1(t \mid X_i)\}$, where the summation is over all observed event time points before $\tilde{T}_i$. The second term is 0 for individuals who are not right-censored by the treatment-unrelated ICE, and is $1/\{\hat{S}_1(\tilde{T}_i \mid X_i) \hat{G}_1(\tilde{T}_i \mid X_i)\}$ for observations with a treatment-unrelated ICE occurred at time $\tilde{T}_i$.

To construct the estimator $\hat{\tau}^{\text{eif}}$, we need to estimate the following nuisance parameters: the propensity score model $e(X)$, the outcome model $\mu_a(X)$ for $a = 0, 1$, and the survival functions for treatment-related and treatment-unrelated ICEs $S_a(t \mid X)$ and $G_a(t \mid X)$, respectively, for $t \leq k$ and $a = 0, 1$. Importantly, as shown in Theorem 3, the consistency of $\hat{\tau}^{\text{eif}}$ does not require correct specification of all four nuisance parameters.

4.2 Asymptotic properties of the EIF-based estimator

We next discuss the asymptotic properties of $\hat{\tau}^{\text{eif}}$. We first introduce additional notation. For $t \leq k$ and $a = 0, 1$, let e^*, G_a^*, μ_a^*, and S_a^* denote the probability limit of the estimated nuisance functions $\hat{e}$, $\hat{G}_a$, $\hat{\mu}_a$, $\hat{S}_a$, respectively, i.e., $\|\hat{e} - e^*\| = o_P(1)$, $\|\hat{G}_a - G_a^*\| = o_P(1)$, $\|\hat{\mu}_a - \mu_a^*\| = o_P(1)$, and $\|\hat{S}_a - S_a^*\| = o_P(1)$. If a given nuisance model is correctly specified, its corresponding limit equals the true function. For example, if the propensity score model is consistent, then $e^* = e$, and similar results hold for the other three nuisance components.

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In the following theorem, we provide the double robustness of the EIF-based estimator $\hat{\tau}^{\mathrm{eif}}$.

THEOREM 3 (DOUBLE ROBUSTNESS OF $\hat{\tau}^{\mathrm{eif}}$) *Under Assumptions 1 and 2, $\hat{\tau}^{\mathrm{eif}}$ is doubly robust in the sense that it is consistent for τ if either $\{e^*(X) = e(X), G_a^*(t \mid X) = G_a(t \mid X)\}$ or $\{\mu_a^*(X) = \mu_a(X), S_a^*(t \mid X) = S_a(t \mid X)\}$ for $t \leq k$ and $a = 0, 1$.*

Theorem 3 shows that $\hat{\tau}^{\mathrm{eif}}$ is consistent if at least one of the following two sets of nuisance parameters are consistently estimated: (1) the outcome model $\mu_a(X)$ and the survival function for the treatment-related ICE $S_a(t \mid X)$; (2) the propensity score model $e(X)$ and the survival function for the treatment-unrelated ICE $G_a(t \mid X)$, for $t \leq k$ and $a = 0, 1$. When our data is from an RCT, i.e., the propensity score $e(X)$ is known by design, so $\hat{e}(X)$ can be correctly specified. Consequently, the EIF-based estimator $\hat{\tau}^{\mathrm{eif}}$ is a consistent estimator for τ if either $G_a(t \mid X)$ is consistently estimated, or both $\mu_a(X)$ and $S_a(t \mid X)$ are consistently estimated, for $t \leq k$ and $a = 0, 1$.

To conduct statistical inference, we provide the asymptotic distribution of $\hat{\tau}^{\mathrm{eif}}$. We first introduce three technical conditions and then state the asymptotic result in a theorem.

ASSUMPTION 3 (CONSISTENCY OF THE NUISANCE PARAMETERS) *Assume that either $\{e^*(X) = e(X), G_a^*(t \mid X) = G_a(t \mid X)\}$ or $\{\mu_a^*(X) = \mu_a(X), S_a^*(t \mid X) = S_a(t \mid X)\}$ for $t \leq k$ and $a = 0, 1$ is satisfied.*

ASSUMPTION 4 (DONSKER CONDITION) *The class of functions $\{(e, G_a, \mu_a, S_a) : ||e - e^*|| < \delta, ||G_a - G_a^*|| < \delta, ||\mu_a - \mu_a^*|| < \delta, ||S_a - S_a^*|| < \delta\}$ is Donsker for some $\delta > 0$.*

ASSUMPTION 5 (CONVERGENCE RATES OF NUISANCE PARAMETERS) *The convergence rate of the nuisance parameters estimation satisfies $\{||\hat{e} - e^*|| + ||\hat{G}_a - G_a^*||\}\{||\hat{\mu}_a - \mu_a^*|| + ||\hat{S}_a - S_a^*||\} = o_P(n^{-1/2})$ for $a = 0, 1$.*

Assumption 3 requires either the propensity score and survival function of the treatment-unrelated ICE or the outcome and survival function of the treatment-related ICE to be consistently estimated. It guarantees the consistency of $\hat{\tau}^{\mathrm{eif}}$. Assumption 4 imposes restrictions on the nuisance model complexity and is a standard regularity condition (Van der Vaart, 2000). We can also employ flexible machine learning models with cross-fitting techniques in the estimation of nuisance parameters to relax the Donsker condition (Pfanzagl and Wefelmeyer, 1985; Klaassen, 1987; Zheng and van der

Laan, 2011; Chernozhukov et al., 2018). Finally, Assumption 5 imposes additional restrictions on the rate of convergence of the nuisance parameters, in addition to all of them being consistently estimated.

THEOREM 4 (ASYMPTOTIC DISTRIBUTION) *Under Assumptions 1– 5, the EIF-based estimator satisfies*

$$n^{1/2}(\hat{\tau}^{\mathrm{eif}} - \tau) \;=\; n^{-1/2}\sum_{i=1}^{n} D_\tau(O_i) + o_P(1).$$

The estimator $\hat{\tau}^{\mathrm{eif}}$ is a consistent and asymptotically Normal estimator of τ with asymptotic variance equal to $E\{D_\tau^2(O)\}$, thus achieving the semiparametric efficiency bound.

Therefore, we can construct the variance estimator based on the semiparametric efficiency bound by taking the empirical analog of the plug-in estimation $n^{-1}\sum_{i=1}^{n} \hat{D}_\tau^2(O_i)$. We can also use a nonparametric bootstrap to estimate variance and conduct statistical inference if the nuisance estimators satisfy certain smoothness conditions.

4.3 Comparing the estimators

In real data analysis, we recommend implementing and comparing all four proposed estimators to assess whether they provide coherent scientific implications. Theoretical comparisons among these estimators primarily focus on two key dimensions: robustness to nuisance model misspecification and asymptotic efficiency. In practice, examining how the point estimates differ across these estimators can provide insight into the presence of nuisance model misspecification. Specifically, certain pairwise differences among the estimators can serve as informal diagnostics. For example, if $e(X)$ is correctly specified, the difference between $\hat{\tau}^{\mathrm{ipw}}$ and $\hat{\tau}^{\mathrm{aug}}$ should converge to zero. Similarly, if $\mu_a(X)$ and $S_a(k \mid X)$ are correctly specified, the difference between $\hat{\tau}^{\mathrm{out}}$ and $\hat{\tau}^{\mathrm{aug}}$ should converge to zero. Finally, if $G_a(t \mid X)$ is correctly specified, the difference between $\hat{\tau}^{\mathrm{eif}}$ and $\hat{\tau}^{\mathrm{aug}}$ should converge to zero. Therefore, when implementing all four estimators in practice, the observed difference among them may serve as an informal diagnostic tool to detect possible nuisance model misspecification. We provide more details in Section A.1 in the supplementary material.

Among the four estimators, a key comparison lies between the EIF-based estimator $\hat{\tau}^{\mathrm{eif}}$ with the augmented weighting estimator $\hat{\tau}^{\mathrm{aug}}$. On the one hand, $\hat{\tau}^{\mathrm{eif}}$ is more robust and asymptotically efficient: it allows for misspecification of the censoring model $C \mid A, X$ and it achieves the semi-

parametric efficiency bound under correct nuisance specification. Continuing the intuition discussed in Section 3.4, $\hat{\tau}^{\text{aug}}$ only orthogonalizes the part corresponding to $A \mid X$ but not $C \mid X, A$, making it robust only to misspecification of the $A \mid X$ model, not the $C \mid X, A$ model. In contrast, $\hat{\tau}^{\text{eif}}$ accounts for both possible sources of misspecification, leading to greater robustness and efficiency. On the other hand, $\hat{\tau}^{\text{aug}}$ is more straightforward to implement in practice, as it only requires the estimation of $S_a(k \mid X)$ and $G_a(k \mid X)$ at time k for $a = 0, 1$, while $\hat{\tau}^{\text{eif}}$ requires consistent estimation of the entire survival curves $S_a(t \mid X)$ and $G_a(t \mid X)$ for $t \leq k$ and $a = 0, 1$. We consider the choice between $\hat{\tau}^{\text{eif}}$ and $\hat{\tau}^{\text{aug}}$ as a trade-off between implementation simplicity and robustness and efficiency of the estimators.

Finally, we note the theoretical possibility of applying a martingale-based correction to the basic weighting estimator $\hat{\tau}^{\text{ipw}}$, in a manner analogous to the correction in the EIF-based estimator $\hat{\tau}^{\text{eif}}$ compared with $\hat{\tau}^{\text{aug}}$. Such a corrected estimator would be robust to misspecification of $G_a(t \mid X)$. However, it remains less attractive in practice: it is neither robust to misspecification of the propensity score nor asymptotically efficient, and it lacks the implementation simplicity of $\hat{\tau}^{\text{aug}}$. For these reasons, we do not recommend it, though we include its explicit form in Section A.2 of the supplementary material only for theoretical completeness.

4.4 Simulation results

We conduct Monte Carlo simulations to evaluate the finite-sample performance of four estimators under various combinations of correctly specified and misspecified nuisance models. Consistent with our theory, $\hat{\tau}^{\text{eif}}$ demonstrates the greatest robustness across all misspecification scenarios, maintaining low bias and valid coverage even when multiple nuisance models are incorrect. We relegate the detailed results to Section B in the supplementary material.

5   Analyzing two phase-3 trials

5.1   Data analysis

In this section, we re-analyze data from two trials on systemic lupus erythematosus (Morand et al., 2023; Petri et al., 2023). Both trials are double-blinded, randomized, placebo-controlled phase-3 trials. There are three treatment arms: 2mg baritinib, 4mg baritinib, and placebo. The primary outcome in both studies is the Systemic lupus erythematosus Responder Index 4 (SRI4) at week 52, a

binary composite endpoint that reflects clinical response. A participant is classified as a responder if they show a predefined improvement in disease activity, without overall worsening or the emergence of significant disease activity in new organ systems. Baseline covariates used for model fitting include geographic region, baseline corticosteroid use, and the Physician's Global Assessment score measured at baseline.

A substantial proportion of participants in both trials experienced ICEs: 218 out of 760 in one trial and 211 out of 775 in the other. As described in Section 1.2, we classify these ICEs into two categories: treatment-related ICEs (82.6% and 84.4% in the two trials, respectively) and treatment-unrelated ICEs (17.4% and 15.6%). We conduct separate comparisons of the 2mg and 4mg baricitinib treatment arms versus the placebo group. For each comparison, we apply all four estimators: $\hat{\tau}^{\text{out}}$, $\hat{\tau}^{\text{ipw}}$, $\hat{\tau}^{\text{aug}}$, and $\hat{\tau}^{\text{eif}}$. We use logistic regression to estimate the propensity score and outcome models, and use Cox proportional hazards regression to separately estimate the survival functions for the two types of ICEs. We conduct variance estimation and inference using a nonparametric bootstrap with 500 replicates. Table 2 presents the resulting point estimates, their estimated standard errors, and corresponding p-values.

Table 2: Treatment effect of Baricitinib on the primary outcome SRI4. The first four columns report the results of Trial 1 and the last four columns report those of Trial 2. The first three rows report the point estimators, standard errors, and the p-value of the composite outcome average treatment effect corresponding to the 2mg treatment arm, and the last three rows report those of the 4mg treatment arm. For each trial and each treatment arm, we report the results based on all four estimators.

		Trial 1 (Petri et al., 2023)				Trial 2 (Morand et al., 2023)			
		$\hat{\tau}^{\text{out}}$	$\hat{\tau}^{\text{ipw}}$	$\hat{\tau}^{\text{aug}}$	$\hat{\tau}^{\text{eif}}$	$\hat{\tau}^{\text{out}}$	$\hat{\tau}^{\text{ipw}}$	$\hat{\tau}^{\text{aug}}$	$\hat{\tau}^{\text{eif}}$
2mg	point	0.030	0.029	0.026	0.026	0.019	0.019	0.022	0.022
	se	0.042	0.043	0.042	0.043	0.042	0.043	0.043	0.042
	p-value	0.479	0.504	0.534	0.540	0.643	0.662	0.602	0.606
4mg	point	0.113	0.120	0.115	0.113	-0.002	-0.002	-0.002	-0.002
	se	0.046	0.046	0.046	0.046	0.042	0.042	0.042	0.042
	p-value	0.013	0.008	0.012	0.013	0.961	0.962	0.966	0.969

5.2 Interpretation of the statistical results

Across both trials and treatment arms, the point estimates and p-values from the four methods are generally consistent. Our results suggest a statistically significant positive effect of 4mg baricitinib on the SRI4 outcome in Trial 1, while in Trial 2, the effect is not significant and the point estimate is slightly negative. No significant treatment effect is observed for the 2 mg baricitinib dose in either trial. As discussed in Section 4.3, though not a formal statistical test, qualitatively, the robustness of estimates across the four estimators in Table 2 provides empirical evidence that our nuisance models may not be severely misspecified.

5.3 Comparison with ad-hoc methods

Next, we use the two commonly used ad-hoc methods and compare them with our proposed methods. The first method is the non-responder imputation method that assigns an outcome as 0 whenever an ICE occurs. It is equivalent to using the composite outcome strategy that treats all ICEs as treatment-related, leading to a composite outcome equal to 0. The second method naively applies a hypothetical strategy to all ICEs, assuming they are independent of potential outcomes conditional on observed covariates.

Table 3 reports the estimated treatment effect of both treatment arms across the two trials using the inverse probability weighting estimator. The non-responder imputation method generally yields slightly smaller effect estimates than our proposed methods, although the differences are modest, likely due to the relatively low proportion of treatment-unrelated ICEs in both trials. Nevertheless, our proposed approach targets a clinically more meaningful causal estimand. The second ad hoc method naively applies the hypothetical strategy to all ICEs, assuming that their occurrence is conditionally independent of the potential outcomes given baseline covariates. This assumption is untestable and likely violated in practice. For example, treatment discontinuation due to adverse events or lack of efficacy is plausibly related to a patient's potential outcome. As shown in Table 3, this method produces treatment effect estimates that differ substantially from those obtained using our proposed approach, potentially leading to misleading clinical conclusions. These empirical findings are consistent with the large-sample bias observed in the simulation study and underscore the importance of using appropriate strategies tailored to different types of ICEs.

Table 3: Treatment effect of Baricitinib on the primary outcome SRI4 using non-responder imputation (NRI) and hypothetical strategy (HS). The first two columns report the results of Trial 1 and the last two columns report those of Trial 2. The first three rows report the point estimators, standard errors, and the p-value of the estimated treatment effect corresponding to the 2mg treatment arm, and the last three rows report those of the 4mg treatment arm. For each trial and each treatment arm, we report the results based on the inverse probability-weighting estimator.

		Trial 1		Trial 2	
		NRI	HS	NRI	HS
2mg	point	0.039	0.011	0.010	0.022
	se	0.043	0.049	0.042	0.050
	p-value	0.362	0.815	0.817	0.654
4mg	point	0.093	0.073	-0.008	0.044
	se	0.044	0.050	0.041	0.051
	p-value	0.036	0.147	0.847	0.382

6 Future directions

In this study, we address the challenges posed by ICEs in RCTs by proposing methods to handle competing ICEs. We classify ICEs into treatment-related and treatment-unrelated events and apply different strategies to identify a clinically meaningful causal effect. For treatment-related ICEs, which are often informative about a patient's outcome, we use a composite variable strategy that assigns an outcome value indicative of treatment failure. For treatment-unrelated ICEs, we apply a hypothetical strategy, assuming their timing is conditionally independent of the outcome given treatment and baseline covariates, and envisioning a scenario in which such events do not occur. The central thesis of this paper is to address the challenge of competing ICEs, where the first ICE censors all subsequent ones. In this paper, we propose a principled framework that carefully formulates the estimand, establishes its nonparametric identification and semiparametric estimation theory, and introduces weighting, outcome regression, and doubly robust estimators. While our proposed framework provides a rigorous and flexible approach for handling competing ICEs in RCTs, several challenges and extensions remain open for future research.

6.1 Data collection and ICE classification

Our proposed methods have broad applicability across various therapeutic areas, including immunology, oncology, and cardiology, where treatment discontinuation and other ICEs frequently occur. However, the effectiveness of these approaches relies on the accurate classification of ICEs, which should be performed in collaboration with clinicians to ensure clinical relevance in trial analyses. To support this, a modernized case report form is needed to enable more granular documentation of the timing, reasons, and magnitude of treatment discontinuation. For example, the reason for the event should be specified, such as discontinuation due to toxicity versus lack of efficacy. In some cases, the event may need to meet a threshold of magnitude, such as the use of additional medication exceeding a specified duration or dose. Additionally, the timing of the event may be relevant, particularly in relation to its proximity to outcome assessment. Fortunately, a cross-industry PHUSE working group is tackling this problem, and a recommended new case report form will be available soon (PHUSE Working Group, 2024).

6.2 Random K

In practice, the measurement of the outcome of interest Y does not necessarily happen at a fixed point k. For instance, the time K that a patient visits the clinic and takes the measurement can be treated as a random variable independent of treatment A, potential outcomes $Y(a)$, and both types of ICEs $T(a)$ and $C(a)$ for $a = 0, 1$. For a random K, the analogous formulas to both the previous identification formulas (2) and (3) hold, with a replacement of k to K, i.e.,

$$
\begin{aligned}
\tau &= E\left\{\mu_1(X)S_1(K \mid X) - \mu_0(X)S_0(K \mid X)\right\} & (9) \\
&= E\left[\frac{AY\mathbb{1}(T \wedge C > K)}{e(X)G_1(K \mid X)} - \frac{(1-A)Y\mathbb{1}(T \wedge C > K)}{\{1-e(X)\}G_0(K \mid X)}\right]. & (10)
\end{aligned}
$$

If K is a pre-treatment covariate that is observed, the proposed four estimators carry over by replacing the fixed k with the observed values of K. If K is also treated as a post-treatment variable, we can construct a weighting estimator following (10). However, (9) no longer provides a feasible identification formula unless $S_a(K \mid X)$ is identified for $a = 0, 1$. Considering the presence of three competing time-to-event random variables, it becomes necessary to employ competing risks models. We defer this analysis to future work.

Acknowledgement

Supplementary material

The supplementary material includes additional technical details, simulation results, and proofs of all theorems and propositions.

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Supplementary Material

Section A provides additional results on comparing the four proposed estimators and another martingale-corrected weighting estimator, discussed in Section 4.3 of the main paper.

Section B reports detailed results from Monte Carlo simulations that assess the finite-sample performance of our proposed estimators.

Section C provides proofs of all theorems and propositions.

A Additional results

A.1 Pairwise differences between the estimators

As discussed in Section 4.3, the observed differences among the four estimators provide insight into the presence of nuisance model misspecification. To illustrate the idea, consider the treated arm as an example. Let $\hat{\mu}_1^{\dagger}$ denote the treated arm counterpart in $\hat{\tau}^{\dagger}$ for $\dagger \in \{\text{out, ipw, aug, eif}\}$, and let $\xrightarrow{\text{P}}$ denote convergence in probability. The probability limits of the pairwise differences between these estimators are given by

$$
\begin{aligned}
\hat{\mu}_1^{\text{aug}} - \hat{\mu}_1^{\text{ipw}} &\xrightarrow{\text{P}} E\left\{\frac{e^*(X) - e(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\right\}, \\
\hat{\mu}_1^{\text{aug}} - \hat{\mu}_1^{\text{out}} &\xrightarrow{\text{P}} E\left[\frac{e(X)}{e^*(X)}\{\mu_1^*(X)S_1^*(k \mid X) - \mu_1(X)S_1(k \mid X)\}\right], \\
\hat{\mu}_1^{\text{eif}} - \hat{\mu}_1^{\text{aug}} &\xrightarrow{\text{P}} E\left[\frac{e(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\int_0^k \frac{S_1(t \mid X)G_1(t \mid X)}{S_1^*(t \mid X)G_1^*(t \mid X)}\{\mathrm{d}\Lambda_1(t \mid X) - \mathrm{d}\Lambda_1^*(t \mid X)\}\right].
\end{aligned}
$$

These probability limits indicate the impact of nuisance model misspecification on the pairwise comparisons. For example, if $G_1(t \mid X)$ is correctly specified, the expected difference between $\hat{\mu}_1^{\text{eif}}$ and $\hat{\mu}_1^{\text{aug}}$ should be small. Similar logic applies to other comparisons. Therefore, when implementing all four estimators in practice, the observed difference among them may serve as an informal diagnostic tool to detect possible nuisance model misspecification.

A.2 The martingale-corrected weighting estimator

In this subsection, we present the explicit form of the martingale-corrected weighting estimator introduced in Section 4.3. Drawing from the proof of Theorem 2 in Section C.3, if we do not project onto the propensity score nuisance tangent space in Step 2, the following identification formula for

μ_1 holds:

$$\mu_1 = E\left[\frac{A}{e(X)}\left\{\frac{Y1(T \wedge C > k)}{G_1(k \mid X)} + \mu_1(X)S_1(k \mid X)\int_0^{\tilde{T}} \frac{dM_{G_1}(t)}{S_1(t \mid X)G_1(t \mid X)}\right\}\right],$$

which motivates the following estimator for μ_1:

$$\hat{\mu}_1^{\text{mc-ipw}} = n^{-1}\sum_{i=1}^n \frac{A_i Y_i 1(T_i \wedge C_i > k)}{\hat{e}(X_i)\hat{G}_1(k \mid X_i)} + n^{-1}\sum_{i=1}^n \frac{A_i}{\hat{e}(X_i)}\hat{\mu}_1(X_i)\hat{S}_1(k \mid X_i)\int_0^{\tilde{T}_i} \frac{dM_{\hat{G}_1}(t)}{\hat{S}_1(t \mid X_i)\hat{G}_1(t \mid X_i)}.$$

The control counterpart, $\hat{\mu}_0^{\text{mc-ipw}}$, is defined analogously, and the estimator for τ is given by $\hat{\tau}^{\text{mc-ipw}} = \hat{\mu}_1^{\text{mc-ipw}} - \hat{\mu}_0^{\text{mc-ipw}}$.

Under Assumuptions 1 and 2, and assuming correct specification of $e(X)$, the estimator $\hat{\tau}^{\text{mc-ipw}}$ is consistent for τ if either $G_a(t \mid X)$ is correct, or both $\mu_a(X)$ and $S_a(t \mid X)$ are correct for $t \leq k$ and $a = 0, 1$. Although the martingale correction enhances robustness to misspecification of $G_a(t \mid X)$, $\hat{\tau}^{\text{mc-ipw}}$ is still less attractive than $\hat{\tau}^{\text{eif}}$: it does not achieve the efficiency bound and is not robust to misspecification of $e(X)$. Moreover, it does not inherit the implementation simplicity of $\hat{\tau}^{\text{aug}}$. In particular, it requires estimating the full survival curves for both the treatment-unrelated ICEs $G_a(t \mid X)$ and treatment-related ICEs $S_a(t \mid X)$ over $t \leq k$, making it computationally demanding without offering clear practical advantages.

B Simulation

In this section, we conduct Monte Carlo simulations to study the finite sample performance of our proposed estimators.

B.1 Data generating processes

We first generate the covariates $X = (X_1, X_2, X_3)^{\text{T}} \in \mathbb{R}^3$ from three independent standard Gaussian distributions and denote $\tilde{X}_j = \{(X_j + 2)^2 - 1\}/\sqrt{12}$ for $j = 1, 2, 3$. Next, we generate the treatment assignment following $A \mid X \sim \text{Bernoulli}(\{e(X)\})$ with $e(X)$ being the propensity score model, and generate the potential outcomes following $Y(a) \mid X \sim \mathcal{N}(\mu_a(X), \sigma_a^2)$ with $\mu_a(X)$ being the outcome model for $a = 0, 1$. We then generate the potential values of the treatment-related ICE survival time

$T(a)$ from the distribution with a survival function

$$S_a(t \mid X) = \exp[-0.002t^{1.2}\exp\{\gamma_a(X)\}]$$

and the potential values of the treatment-unrelated ICE survival time $C(a)$ from the distributions with a survival function

$$G_a(t \mid X) = \exp[-\varrho_a(t)\exp\{\delta_a(X)\}],$$

for $a = 0, 1$. For each of the nuisance parameters, we consider two scenarios when it will be correctly modeled and misspecified, therefore, we generate data following two different choices of each. We summarize the detailed data-generating choices in Table S1.

Table S1: Model choices for the nuisance parameters

	Correctly specified	Misspecified
$\text{logit}\{e(X)\}$	$(X_1 + X_2 + X_3)/5$	$1(X_1 \geq 0)\{\exp(\tilde{X}_2) - X_2(1 + \tilde{X}_3)\} - \exp(\tilde{X}_2)$
$\mu_1(X)$	$2(X_1 + X_2 + X_3)$	$1(X_1 \geq 0)\{X_2 + \exp(X_2)\tilde{X}_3 - \tilde{X}_2\} + \tilde{X}_2$
$\mu_0(X)$	$X_1 + X_2 + X_3$	$-\tilde{X}_1 - 1(X_1 > 0.5)\tilde{X}_2 + 1(X_1 < -0.5)X_2^2\log(|X_3| + 1)$
σ_a	$0.1(a + 1)$	1
$\gamma_1(X)$	$0.1(X_1 + 2X_2 - 2X_3)$	$0.1(X_1^2 X_2 - X_2 - 1) + 1(X_3 \neq 0)X_2\log(10X_3^2)$
$\gamma_0(X)$	$0.1(X_1 - 2X_2 + 2X_3)$	$0.01(-\tilde{X}_1 + \tilde{X}_2 + \tilde{X}_3)$
$\delta_1(X)$	0	$0.1(X_1^2 X_2 - X_2 - 1) + 1(X_3 \neq 0)X_2\log(10X_3^2)$
$\delta_0(X)$	0	0
$\varrho_a(t)$	$-0.01t^{1.2}$	$-0.01at^{1.2} + 0.6 * 0.01^{1/1.2}(1 - a)t$

We consider five data-generating regimes: all four models are correctly specified, misspecified e and correct (G, μ, S), misspecified (e, G) and correct (μ, S), misspecified (μ, S) and correct (e, G), and all four models are misspecified. Let $Y = AY(1) + (1 - A)Y(0)$, $T = AT(1) + (1 - A)T(0)$, and $C = AC(1) + (1 - A)C(0)$. Generate the observed event time as $T \wedge C \wedge k$, the observed event type indicator, and the observed outcome Y if $T \wedge C > k$.

B.2 Simulation results

We compare the finite sample performance of the outcome estimator $\hat{\tau}^{\text{out}}$, the weighting estimator $\hat{\tau}^{\text{ipw}}$, the augmented weighting estimator $\hat{\tau}^{\text{aug}}$, and the EIF estimator $\hat{\tau}^{\text{eif}}$ based on 1000 Monte Carlo

samples with a sample size of $n = 1000$. When fitting the nuisance models, we use logistic regression of A on X to estimate the propensity score model, the linear regression of Y on X on the subsample $A = a, T \wedge C > k$ to estimate the outcome model, and the Cox proportional hazard regression of T and C on X on the subsample $A = a$ to estimate the treatment-related ICE survival model and the censoring model, respectively, for $a = 0, 1$. We use X in all regression models, therefore, when the true data-generating processes involve non-linear functions of X, the fitted nuisance models suffer from misspecification. We evaluate the performance of the four estimators with reported bias, standard deviation, and coverage probability using a nonparametric bootstrap with 200 bootstrap samples in Table S2.

Table S2: Finite sample performance of the four estimators. For each estimator, we report the finite-sample bias, standard deviation (SD), and the coverage rate (CR) of a 95% confidence interval, which is constructed using a nonparametric bootstrap with 200 bootstrap iterations. Each row corresponds to a different data-generating regime.

	$\hat{\tau}^{\text{out}}$			$\hat{\tau}^{\text{ipw}}$			$\hat{\tau}^{\text{aug}}$			$\hat{\tau}^{\text{eif}}$		
	Bias	SD	CR	Bias	SD	CR	Bias	SD	CR	Bias	SD	CR
all_correct	0.003	0.100	0.989	0.005	0.154	0.977	0.004	0.152	0.980	0.004	0.110	0.982
e_wrong	−0.002	0.134	0.978	−0.338	0.527	0.916	−0.003	0.479	0.961	0.000	0.234	0.979
e_G_wrong	−0.002	0.130	0.985	−0.194	1.591	0.831	0.141	1.559	0.972	−0.013	0.354	0.969
μ_S_wrong	−0.085	0.170	0.936	−0.009	0.186	0.974	−0.009	0.186	0.974	−0.012	0.176	0.972
all_wrong	0.230	0.233	0.837	0.660	5.799	0.898	0.850	5.782	0.967	0.573	3.022	0.919

Consistent with our theoretical results, all estimators have a finite sample bias close to zero when all models are correctly specified. When e is misspecified and (G, μ, S) are correct, the weighting estimator $\hat{\tau}^{\text{ipw}}$ is inconsistent while the other three estimators have small finite sample bias. Under the regime when e and G are misspecified, both $\hat{\tau}^{\text{ipw}}$ and $\hat{\tau}^{\text{aug}}$ perform poorly as they have larger finite sample biases, $\hat{\tau}^{\text{out}}$ and $\hat{\tau}^{\text{eif}}$ show small finite sample biases as expected. When (μ, S) are misspecified, the outcome estimator $\hat{\tau}^{\text{out}}$ has a relatively large bias, while all other three estimators have near-zero biases. All estimators have non-negligible finite sample bias when all nuisance models are misspecified. $\hat{\tau}^{\text{eif}}$ is most robust to model misspecifications across all different regimes.

$\hat{\tau}^{\text{eif}}$ shows a relatively smaller standard deviation compared to $\hat{\tau}^{\text{ipw}}$ and $\hat{\tau}^{\text{aug}}$ in the regimes where all estimators are consistent. The outcome estimator $\hat{\tau}^{\text{out}}$ always has the smallest standard deviation when (μ, S) is correctly specified. Both $\hat{\tau}^{\text{ipw}}$ and $\hat{\tau}^{\text{aug}}$ have larger standard deviations across all regimes in which they are consistent. Furthermore, confidence intervals constructed using the nonparametric bootstrap yield valid coverage rates for the corresponding consistent estimators

in their respective regimes.

Next, we evaluate two ad-hoc methods commonly used in clinical trials with ICEs, demonstrating through simulations that they are biased in estimating the clinically relevant causal parameter. The first method is the non-responder imputation method that assigns an outcome as 0 whenever an ICE occurs. It is equivalent to using the composite outcome strategy that treats all ICEs as treatment-related, leading to a composite outcome equal to 0. The second method naively applies a hypothetical strategy to all ICEs, assuming they are independent of potential outcomes conditional on observed covariates. We generate data under the "$\mu\_S\_$wrong" regime, ensuring correct specification of both the propensity score $e(X)$ and the treatment-unrelated ICE survival model $G_a(t \mid X)$ for $a = 0, 1$. Based on 1000 Monte Carlo simulations with a sample size of $n = 1000$, the inverse probability-weighting estimator using the non-responder imputation method exhibits a finite sample bias of -1.195 with a standard deviation of 0.077, and that using the hypothetical strategy for all ICEs has a bias of 1.188 with a standard deviation of 0.388. Both ad-hoc methods yield inconsistent estimators.

C   Proofs

C.1   Proof of Theorem 1

First, equation (2) holds because its left-hand side equals

$$
\begin{aligned}
& E[E\{Y(1)1(T(1) > k) \mid X\}] \\
= \ & E[E\{Y1(T > k) \mid X, A = 1\}] \\
= \ & E\{E(Y \mid T > k, X, A = 1)\mathrm{pr}(T > k \mid X, A = 1)\} \\
= \ & E\{E(Y \mid T > k, C > k, X, A = 1)\mathrm{pr}(T > k \mid X, A = 1)\},
\end{aligned}
$$

which is equal to the right-hand side of (2), where the first equality is by the law of iterated expectations, the second equality is by the randomization assumption 1, and the third equality is by the censoring at random assumption 2.

Next, equation (3) holds because its right-hand side equals

$$
E\left[E\left\{\frac{AY1(T \wedge C > k)}{e(X)\mathrm{pr}(C > k \mid X, A = 1)} \mid X\right\}\right]
$$

$$
\begin{aligned}
&= E\left(\frac{1}{e(X)\mathrm{pr}(C > k \mid X, A = 1)} E\left[AY(1)1\{T(1) \wedge C(1) > k\} \mid X\right]\right)\\
&= E\left(\frac{1}{e(X)\mathrm{pr}(C > k \mid X, A = 1)} E(A \mid X) E\left[Y(1)1\{T(1) > k\}1\{C(1) > k\} \mid X\right]\right)\\
&= E\left(\frac{1}{\mathrm{pr}(C > k \mid X, A = 1)} E[1\{C(1) > k\} \mid X] E\left[Y(1)1\{T(1) > k\} \mid X\right]\right)\\
&= E[E\{Y(1)1(T(1) > k) \mid X\}],
\end{aligned}
$$

which is equal to the left-hand side of (3), where the first equality is by the law of iterated expectations, the third equality is by the randomization assumption 1, the fourth equality is by the censoring at random assumption 2, and the last equality is again by the law of iterated expectations. □

C.2   Proof of Proposition 1

We prove that under the correct specification of the censoring model, $\hat{\tau}^{\mathrm{aug}}$ is doubly robust in the sense that it is consistent for τ if either $e^* = e$ or $(\mu_1^* = \mu_1, S_1^* = S_1)$. We have

$$
\begin{aligned}
&E\left\{\frac{AY1(T \wedge C > k)}{e^*(X)G_1(k \mid X)} - \frac{A - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\right\}\\
&= E\left[\frac{E\{AY1(T \wedge C > k) \mid X\}}{e^*(X)G_1(k \mid X)} - \frac{e(X) - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\right]\\
&= E\left\{\frac{e(X)}{e^*(X)}\mu_1(X)S_1(k \mid X) - \frac{e(X) - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\right\}, \qquad\qquad (\mathrm{S1})
\end{aligned}
$$

where the first equality follows from the law of integrated expectations and the second equality follows from similar derivations as in the proof of Theorem 1. Now observe that the final expression of (S1) is equal to μ_1 if either $e^* = e$ or $(\mu_1^* = \mu_1, S_1^* = S_1)$. Therefore, we have

$$
E\left\{\frac{AY1(T \wedge C > k)}{e^*(X)G_1(k \mid X)} - \frac{A - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X) - \mu_1\right\} = 0
$$

if either $e^* = e$ or $(\mu_1^* = \mu_1, S_1^* = S_1)$ holds. A parallel argument applies to the control counterpart. Therefore, combining the treated and control components, we conclude that $\hat{\tau}^{\mathrm{aug}}$ is consistent for τ if either the propensity score model is correct, or the outcome and survival models for the treatment-related ICE are both correct. This establishes the double robustness of $\hat{\tau}^{\mathrm{aug}}$. □

C.3 Proof of Theorem 2

We follow the semiparametric theory in Bickel et al. (1993) to derive the EIF for μ_1. As discussed in Section 4, we have two levels of coarsening of the full data $(X, Y^{\mathrm{cp}}(1), Y^{\mathrm{cp}}(0))$, one is because the treatment-unrelated ICE time $C(a)$ is censoring $T(a) \wedge k$, and the other is due to the treatment assignment. Following the steps in Hubbard et al. (2000), we first consider the case when every observation is assigned to the treatment group, i.e., when there is no missingness generated by the treatment assignment, and then project the derived EIF onto the nuisance tangent space of the propensity score to get the final form of EIF for μ_1.

Step 1. With full data $(X, Y^{\mathrm{cp}}(1), Y^{\mathrm{cp}}(0))$, the estimating equation for μ_1 is $D_{\mathrm{full}} = Y^{\mathrm{cp}}(1) - \mu_1$. Since $Y^{\mathrm{cp}}(1)$ is only observable if $C(1) > T(1) \wedge k$, the full data is not available even if all corresponding potential outcomes under treatment $A = 1$ are observed, and the observed data is

$$O(1) \;=\; (X, \Delta(1), \tilde{T}(1), \Delta(1)Y^{\mathrm{cp}}(1)) \sim P_1,$$

where $\Delta(1) = 1(C(1) > T(1) \wedge k)$ is the missing indicator with $\Delta(1) = 1$ if $Y^{\mathrm{cp}}(1)$ is observed and $\Delta(1) = 0$ otherwise, and $\tilde{T}(1) = T(1) \wedge C(1) \wedge k$ is the observed event time with $\tilde{T}(1) = T(1) \wedge k$ if $\Delta(1) = 1$, $Y^{\mathrm{cp}}(1)$ is observed, and $\tilde{T}(1) = C(1)$ if $\Delta(1) = 0$, $Y^{\mathrm{cp}}(1)$ is missing. An identification formula for μ_1 is

$$\mu_1 = E\left\{ \frac{\Delta(1)Y^{\mathrm{cp}}(1)}{G_1(\tilde{T}(1) \mid X)} \right\},$$

where $G_1(t \mid X) = \mathrm{pr}(C(1) > t \mid X)$ is the probability of not censoring up to time t conditioning on the covariates. We can write the IPCW estimating equation as

$$D_{\mathrm{IPCW}} = \frac{\Delta(1)\{Y^{\mathrm{cp}}(1) - \mu_1\}}{G_1(\tilde{T}(1) \mid X)},$$

and have $E(D_{\mathrm{IPCW}}) = 0$ by the law of iterated expectations and the censoring at random assumption.

Next, we follow the steps in van der Laan and Rubin (2007) to derive the EIF for μ_1 when the observed data is $O(1) = (X, \Delta(1), \tilde{T}(1), \Delta(1)Y^{\mathrm{cp}}(1))$. For ease of notation, we omit the subscripts, superscripts, or numbers in parenthesis (1) that indicate the potential outcomes under the treatment $A = 1$ in the following derivation, so the dependence on the treatment arm is implicit. For ease of notation, denote $T^1 = T \wedge k$.

Let $T(P)$ denote the tangent space which is the whole Hilbert space $L_0^2(P)$ since our model is nonparametric. The tangent space can be written as a direct sum of three components $T = T_X \oplus T_{\mathrm{F}} \oplus T_{\mathrm{CAR}}$ with

$$
\begin{aligned}
T_X &= \{h(X) \in L_0^2(P) : E\{h(X)\} = 0\}, \\
T_{\mathrm{F}} &= \{h(O) \in L_0^2(P) : E\{h(O) \mid C, X\} = 0\}, \\
T_{\mathrm{CAR}} &= \{h(O) \in L_0^2(P) : E\{h(O) \mid Y^{\mathrm{cp}}, T^1, X\} = 0\},
\end{aligned}
$$

where T_X, T_{F}, and T_{CAR} are orthogonal to each other due to the censoring at random assumption and the factorization of the observed data. These tangent spaces are generated from scores of submodels that perturb the marginal distribution of X, the conditional distribution of $Y^1 \mid X$, and the conditional censoring probability $C \mid X$, respectively. Due to the orthogonality, we have the decomposition of any $h(O) \in L_0^2(P)$ as

$$
\begin{aligned}
h(O) &= \Pi\{h \mid T(P)\} \\
&= \Pi\{h \mid T_X(P)\} + \Pi\{h \mid T_{\mathrm{F}}(P)\} + \Pi\{h \mid T_{\mathrm{CAR}}(P)\}.
\end{aligned}
$$

Let $D(O)$ denote the efficient influence function for μ_1. By the results in Chapter 1.4 of van der Laan and Robins (2003), we have: (1) $D(O)$ should be orthogonal to the nuisance tangent space T_{CAR}, thus $\Pi\{D(O) \mid T_{\mathrm{CAR}}(P)\} = 0$; (2) $D(O)$ can be rewritten as

$$
D = D_{\mathrm{IPCW}} - \Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{CAR}}(P)\},
$$

thus

$$
\begin{aligned}
\Pi\{D \mid T_{\mathrm{F}}(P)\} &= \Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{F}}(P)\} - \Pi\{\Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{CAR}}(P)\} \mid T_{\mathrm{F}}(P)\} \\
&= \Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{F}}(P)\}
\end{aligned}
$$

where the last equality is by the fact that T_{F} and T_{CAR} are orthogonal to each other, and similarly, $\Pi\{D \mid T_X(P)\} = \Pi\{D_{\mathrm{IPCW}} \mid T_X(P)\}$.

These projections provide us with two different ways to compute the EIF D: (1) directly com-

pute the projections $\Pi\{D_{\mathrm{IPCW}} \mid T_X(P)\}$ and $\Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{F}}(P)\}$ and sum them up; (2) compute the projection $\Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{CAR}}(P)\}$ and subtract it from D_{IPCW}. In the classic survival outcome problem, these two methods are symmetric since T and C are censoring each other thus the projections on $T_{\mathrm{F}}(P)$ and $T_{\mathrm{CAR}}(P)$ are very similar. However, due to the complication generated by Y in our setting, the second approach is easier, since the tangent space $T_{\mathrm{F}}(P)$ is hard to compute.

We next compute $\Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{CAR}}(P)\}$. By Theorem 1.1 in van der Laan and Robins (2003),

$$T_{\mathrm{CAR}}(P) = \overline{\left\{ \int H(t, \mathcal{F}(t)) \mathrm{d}M_G(t) \text{ for all functions } H(t, \mathcal{F}(t)) \right\}} \cap L_0^2(P),$$

and the projection of a function $h(O)$ onto $T_{\mathrm{CAR}}(P)$ is

$$\Pi\{h(O) \mid T_{\mathrm{CAR}}(P)\} = \int_0^{\tilde{T}} \{E(h(O) \mid \mathrm{d}A(t) = 1, \mathcal{F}(t)) - E(h(O) \mid \mathrm{d}A(t) = 0, \mathcal{F}(t))\} \mathrm{d}M_G(t),$$

where $A(t) = 1(C \leq t)$ is the indicator of whether censoring happens up until time t (define $C = \infty$ if $C > T^1$ so that C is always observed), $\mathcal{F}(t) = (\bar{A}(t-), X)$ is the history observed up to time t, and $\mathrm{d}M_G(t) = 1(C \in \mathrm{d}t, \Delta = 0) - 1(\tilde{T} \geq t)\mathrm{d}\Lambda(t \mid X)$ is the Doob–Meyer martingale of the counting process of censoring C. $E(D_{\mathrm{IPCW}} \mid \mathrm{d}A(t) = 1, \mathcal{F}(t)) = 0$ by the definition of D_{IPCW}, thus we only need to compute $E(D_{\mathrm{IPCW}} \mid \mathrm{d}A(t) = 0, \mathcal{F}(t))$, which plus μ_1 is equal to

$$
\begin{aligned}
&E\left\{ \frac{\Delta Y^{\mathrm{cp}}}{G(\tilde{T} \mid X)} \mid \mathrm{d}A(t) = 0, \mathcal{F}(t) \right\} \\
=~&E\left\{ \frac{\Delta Y^{\mathrm{cp}}}{G(\tilde{T} \mid X)} \mid T^1 \geq t, C \geq t, X \right\} \\
=~&E\left\{ \frac{\Delta Y^{\mathrm{cp}}}{G(\tilde{T} \mid X)} \mid T^1 \geq t, X \right\} / G(t \mid X) \\
=~&E\left\{ \frac{Y^{\mathrm{cp}}}{G(T \wedge k \mid X)} \mathrm{pr}(C > T \wedge k \mid T^1 \geq t, T, Y^1, X) \mid T^1 \geq t, X \right\} / G(t \mid X) \\
=~&E\left\{ \frac{Y^{\mathrm{cp}}}{G(T \wedge k \mid X)} \mathrm{pr}(C > T \wedge k \mid X) \mid T^1 \geq t, X \right\} / G(t \mid X) \\
=~&E\left\{ Y^{\mathrm{cp}} \mid T^1 \geq t, X \right\} / G(t \mid X).
\end{aligned}
$$

By the fact that the integration is over $t : t < \tilde{T}$, we have $t < T \wedge k \wedge C$ thus $t > k$. The conditional

expectation

$$
\begin{aligned}
E\left\{Y^{\mathrm{cp}} \mid T^1 \geq t, X\right\} &= E\left\{Y^{\mathrm{cp}} \mid T^1 \geq t, T^1 = T, X\right\} \mathrm{pr}(T^1 = T \mid T^1 \geq t, X) \\
&\quad + E\left\{Y^{\mathrm{cp}} \mid T^1 \geq t, T^1 = k, X\right\} \mathrm{pr}(T^1 = k \mid T^1 \geq t, X) \\
&= E(Y \mid T > k \geq t, X)\mathrm{pr}(T > k \mid T^1 \geq t, X) \\
&= E(Y \mid T > k, X)\mathrm{pr}(T > k \mid T \wedge k \geq t, X) \\
&= E(Y \mid T > k, X)\mathrm{pr}(T > k \mid T \geq t, X) \\
&= \frac{E\{Y1(T > k) \mid X\}}{\mathrm{pr}(T > k \mid X)} \frac{\mathrm{pr}(T > k \mid X)}{\mathrm{pr}(T \geq t \mid X)} \\
&= \frac{E\{Y1(T > k) \mid X\}}{\mathrm{pr}(T \geq t \mid X)}.
\end{aligned}
$$

Therefore, we have

$$
\begin{aligned}
\Pi\{D_{\mathrm{IPCW}} \mid T_{\mathrm{CAR}}(P)\} + \mu_1 &= -\int_0^{\tilde{T}} \frac{E\{Y1(T > k) \mid X\}}{\mathrm{pr}(T \geq t \mid X)} \frac{\mathrm{d}M_G(t)}{G(t \mid X)} \\
&= -E\{Y1(T > k) \mid X\} \int_0^{\tilde{T}} \frac{\mathrm{d}M_G(t)}{S(t \mid X)G(t \mid X)},
\end{aligned}
$$

and thus the EIF assuming $O(1)$ is the observed data is

$$
D = \frac{\Delta Y^{\mathrm{cp}}}{G(\tilde{T} \mid X)} + E(Y^{\mathrm{cp}} \mid X) \int_0^{\tilde{T}} \frac{\mathrm{d}M_G(t)}{S(t \mid X)G(t \mid X)} - \mu_1 \tag{S2}
$$

Step 2. Next, we follow steps in Section 3 of Hubbard et al. (2000) and compute the EIF when the real observed data is $O = (X, A, \Delta, \tilde{T}, \Delta Y^{\mathrm{cp}})$. We need to construct a weighting estimating equation and then subtract its projection onto the nuisance tangent space of the propensity score to get the final form of the EIF. To be clear on the distinction between potential outcomes and the observed values, we add back the dependence on the treatment assignment in (S2) and write it as

$$
D(1) = \frac{\Delta(1)Y^{\mathrm{cp}}(1)}{G_1(\tilde{T}(1) \mid X)} + E(Y^{\mathrm{cp}}(1) \mid X) \int_0^{\tilde{T}(1)} \frac{\mathrm{d}M_{G_1}(t)}{S_1(t \mid X)G_1(t \mid X)} - \mu_1.
$$

A valid weighting estimating equation is

$$
D_{\mathrm{IPW}} = \frac{A}{e(X)}\left\{\frac{\Delta Y^{\mathrm{cp}}}{G_1(\tilde{T} \mid X)} + E(Y^{\mathrm{cp}} \mid X, A = 1) \int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1}(t)}{S_1(t \mid X)G_1(t \mid X)}\right\} - \mu_1.
$$

Further, project this onto the nuisance tangent space of the propensity score, the projection is

$$
\begin{aligned}
\Pi\{D_{\mathrm{IPW}} \mid T_{\mathrm{pscore}}\} &= E\left\{D_{\mathrm{IPW}} \mid A, X\right\} - E\left\{D_{\mathrm{IPW}} \mid X\right\} \\
&= \frac{A - e(X)}{e(X)} E\left\{\frac{\Delta Y^{\mathrm{cp}}}{G_1(\tilde{T} \mid X)} \mid X, A = 1\right\} \\
&= \frac{A - e(X)}{e(X)} E(Y^{\mathrm{cp}} \mid X, A = 1),
\end{aligned}
$$

where the second equality is by the fact that $E\{\mathrm{d}M_{G_1}(t) \mid X, A = 1\} = E\{\mathrm{d}M_{G_1}(t) \mid X\} = 0$, and the last equality is by the censoring at random assumption. Therefore, the EIF

$$
\begin{aligned}
D_1 &= D_{\mathrm{IPW}} - \Pi\{D_{\mathrm{IPW}} \mid T_{\mathrm{pscore}}\} \\
&= \frac{A}{e(X)}\left\{\frac{\Delta Y^{\mathrm{cp}}}{G_1(\tilde{T} \mid X)} + E(Y1(T > k) \mid X, A = 1) \int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1}(t)}{S_1(t \mid X)G_1(t \mid X)}\right\} \\
&\quad - \frac{A - e(X)}{e(X)} E(Y1(T > k) \mid X, A = 1) - \mu_1
\end{aligned}
$$

has the given form in Theorem 2. $\qquad\square$

C.4 Proof of Theorem 3

We prove the result by showing

$$
\begin{aligned}
\mu_1 &= E\left[\frac{A}{e^*(X)}\left\{\frac{Y1(T \wedge C > k)}{G_1^*(k \mid X)} + \mu_1^*(X)S_1^*(k \mid X) \int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1^*}(t)}{S_1^*(t \mid X)G_1^*(t \mid X)}\right\}\right. \\
&\quad \left. - \frac{A - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\right] \qquad\qquad\qquad\qquad\qquad\qquad \text{(S3)}
\end{aligned}
$$

if either $\{e^*(X) = e(X), G_1^*(t \mid X) = G_1(t \mid X)\}$ or $\{\mu_1^*(X) = \mu_1(X), S_1^*(t \mid X) = S_1(t \mid X)\}$ for $t \le k$. Define

$$
\begin{aligned}
\mathcal{T}_1 &= \frac{A}{e^*(X)}\frac{Y1(T \wedge C > k)}{G_1^*(k \mid X)} - \frac{A - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X) - \mu_1(X)S_1(k \mid X), \\
\mathcal{T}_2 &= \frac{A}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X) \int_0^{\tilde{T}} \frac{\mathrm{d}M_{G_1^*}(t)}{S_1^*(t \mid X)G_1^*(t \mid X)}.
\end{aligned}
$$

By the identification formula (2), to prove (S3), it suffices to show $E(\mathcal{T}_1 + \mathcal{T}_2) = 0$ if either $\{e^*(X) = e(X), G_1^*(t \mid X) = G_1(t \mid X)\}$ or $\{\mu_1^*(X) = \mu_1(X), S_1^*(t \mid X) = S_1(t \mid X)\}$ for $t \le k$.

First, we have

$$
\begin{aligned}
E\{\mathrm{d}M_{G_1^*}(t) \mid X\} &= E\{1(C \in \mathrm{d}t, \Delta = 0) \mid X\} - E\{1(\tilde{T} \geq t)\mathrm{d}\Lambda_1^*(t \mid X) \mid X\} \\
&= S_1(t \mid X)G_1(t \mid X)\mathrm{d}\Lambda_1(t \mid X) - S_1(t \mid X)G_1(t \mid X)\mathrm{d}\Lambda_1^*(t \mid X) \\
&= S_1(t \mid X)G_1(t \mid X)\{\mathrm{d}\Lambda_1(t \mid X) - \mathrm{d}\Lambda_1^*(t \mid X)\},
\end{aligned}
$$

and therefore,

$$
\begin{aligned}
E(\mathcal{T}_2 \mid X) &= \frac{e(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)E\left\{\int_0^k \frac{\mathrm{d}M_{G_1^*}(t)}{S_1^*(t \mid X)G_1^*(t \mid X)} \mid X\right\} \\
&= \frac{e(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\int_0^k \frac{S_1(t \mid X)G_1(t \mid X)}{S_1^*(t \mid X)G_1^*(t \mid X)}\{\mathrm{d}\Lambda_1(t \mid X) - \mathrm{d}\Lambda_1^*(t \mid X)\},
\end{aligned}
$$

where the first equality follows from Assumption 1. Next, we have

$$
\begin{aligned}
E(\mathcal{T}_1 \mid X) &= \frac{e(X)G_1(k \mid X)}{e^*(X)G_1^*(k \mid X)}\mu_1(X)S_1(k \mid X) - \frac{e(X) - e^*(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X) - \mu_1(X)S_1(k \mid X) \\
&= \frac{e(X)}{e^*(X)}\left\{\frac{G_1(k \mid X)}{G_1^*(k \mid X)} - 1\right\}\mu_1^*(X)S_1^*(k \mid X) \\
&\quad + \left\{\frac{e(X)G_1(k \mid X)}{e^*(X)G_1^*(k \mid X)} - 1\right\}\{\mu_1(X)S_1(k \mid X) - \mu_1^*(X)S_1^*(k \mid X)\} \\
&= -\frac{e(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\int_0^k \frac{G_1(t \mid X)}{G_1^*(t \mid X)}\{\mathrm{d}\Lambda_1(t \mid X) - \mathrm{d}\Lambda_1^*(t \mid X)\} \\
&\quad + \left\{\frac{e(X)G_1(k \mid X)}{e^*(X)G_1^*(k \mid X)} - 1\right\}\{\mu_1(X)S_1(k \mid X) - \mu_1^*(X)S_1^*(k \mid X)\},
\end{aligned}
$$

where the last equality follows from the Duhamel equation (Gill and Johansen, 1990; Westling et al., 2024). Combing $\mathcal{T}_1$ and $\mathcal{T}_2$, we have

$$
\begin{aligned}
E(\mathcal{T}_1 + \mathcal{T}_2) &= E\{E(\mathcal{T}_1 + \mathcal{T}_2 \mid X)\} \\
&= \frac{e(X)}{e^*(X)}\mu_1^*(X)S_1^*(k \mid X)\int_0^k \left\{\frac{S_1(t \mid X)}{S_1^*(t \mid X)} - 1\right\}\frac{G_1(t \mid X)}{G_1^*(t \mid X)}\{\mathrm{d}\Lambda_1(t \mid X) - \mathrm{d}\Lambda_1^*(t \mid X)\} \\
&\quad + \left\{\frac{e(X)G_1(k \mid X)}{e^*(X)G_1^*(k \mid X)} - 1\right\}\{\mu_1(X)S_1(k \mid X) - \mu_1^*(X)S_1^*(k \mid X)\},
\end{aligned}
$$

which is equal to 0 if either $\{e^*(X) = e(X), G_1^*(t \mid X) = G_1(t \mid X)\}$ or $\{\mu_1^*(X) = \mu_1(X), S_1^*(t \mid X) = S_1(t \mid X)\}$ for $t \leq k$.

By symmetry, the part corresponding to the control arm $a = 0$ also holds, thus the double

robustness in Theorem 3 holds. □

C.5 Proof of Theorem 4

Following the von Mises expansion (Hines et al., 2022), let P and P_n denote the true and empirical distribution of the observed data, respectively, and $\hat{P}_n$ denotes an estimated P, we have

$$n^{1/2}(\hat{\tau}^{\mathrm{eif}} - \tau) \;=\; n^{-1/2}\sum_{i=1}^{n} D_\tau(O_i) + n^{1/2}(P_n - P)\{D_\tau(O, \hat{P}_n) - D_\tau(O)\} - n^{1/2}R(P, \hat{P}_n),$$

where $D_\tau(O, \hat{P}_n)$ is the EIF for τ when plugging in the estimated values of the nuisance parameters and $R(P, \hat{P}_n)$ denotes the higher order remainder term. Under Assumption 4, the empirical process term $n^{1/2}(P_n - P)\{D_\tau(O, \hat{P}_n) - D_\tau(O)\} = o_P(1)$ (Van der Vaart, 2000). The remainder term corresponding to the treatment arm $a = 1$ satisfies

$$
\begin{aligned}
R_1(P, \hat{P}_n) \;=\;& -E\{D_\tau(O, \hat{P}_n)\} - E\{\hat{\mu}_1(X)\hat{S}_1(k \mid X) - \mu_1(X)S_1(k \mid X)\} \\
=\;& -E\left[\frac{A}{\hat{e}(X)}\left\{ \frac{Y1(T \wedge C > k)}{\hat{G}_1(k \mid X)} + \hat{\mu}_1(X)\hat{S}_1(k \mid X)\int_0^k \frac{\mathrm{d}M_{\hat{G}_1}(t)}{\hat{G}_1(t \mid X)\hat{S}_1(t \mid X)} \right\} \right. \\
& \left. - \frac{A - \hat{e}(X)}{\hat{e}(X)}\hat{\mu}_1(X)\hat{S}_1(k \mid X) - \hat{\mu}_1(X)\hat{S}_1(k \mid X) + \hat{\mu}_1(X)\hat{S}_1(k \mid X) - \mu_1(X)S_1(k \mid X) \right] \\
=\;& -E\left[\frac{e(X)}{\hat{e}(X)}\hat{\mu}_1(X)\hat{S}_1(k \mid X)\int_0^k \left\{ \frac{S_1(t \mid X)}{\hat{S}_1(t \mid X)} - 1 \right\}\frac{G_1(t \mid X)}{\hat{G}_1(t \mid X)}\{\mathrm{d}\Lambda_1(t \mid X) - \mathrm{d}\hat{\Lambda}_1(t \mid X)\} \right] \\
& + E\left[\left\{ \frac{e(X)G_1(k \mid X)}{\hat{e}(X)\hat{G}_1(k \mid X)} - 1 \right\}\left\{ \mu_1(X)S_1(k \mid X) - \hat{\mu}_1(X)\hat{S}_1(k \mid X) \right\} \right] \\
=\;& E\left\{ \frac{e(X)}{\hat{e}(X)}\hat{\mu}_1(X)\hat{S}_1(k \mid X)\int_0^k \frac{S_1(t \mid X) - \hat{S}_1(t \mid X)}{\hat{S}_1(t \mid X)}\frac{G_1(t \mid X) - \hat{G}_1(t \mid X)}{\hat{G}_1(t \mid X)}\mathrm{d}t \right\} \\
& + E\left[\frac{e(X)G_1(k \mid X) - \hat{e}(X)\hat{G}_1(k \mid X)}{\hat{e}(X)\hat{G}_1(k \mid X)}\left\{ \mu_1(X)S_1(k \mid X) - \hat{\mu}_1(X)\hat{S}_1(k \mid X) \right\} \right],
\end{aligned}
$$

where the third equality follows from a similar derivation as in the Proof of Theorem 3 and the fourth equality follows from the Duhamel equation (Gill and Johansen, 1990; Westling et al., 2024). Let R_{11} and R_{12} denote the two terms in the last two lines, respectively. For the remainder term to be of small order, we need $R_{11} = o_P(n^{-1/2})$ and $R_{12} = o_P(n^{-1/2})$.

Next, we show that Assumption 5 is a sufficient condition for $R_{11} = o_P(n^{-1/2})$ and $R_{12} = o_P(n^{-1/2})$. In the following discussion, we suppress the dependency of the nuisance functions and their estimated values on X for ease of notation. By the facts that $e\hat{\mu}_1\hat{S}_1(k)/\hat{e}$ is bounded and

$1/\{\hat{S}_1(t)\hat{G}_1(t)\}$ is bounded for any $t \leq k$, we employ the Cauchy–Schwarz inequality to upper bound the term R_{11} by a constant times

$$\int_0^k ||S_1(t) - \hat{S}_1(t)||_2 ||G_1(t) - \hat{G}_1(t)||_2 \mathrm{d}t,$$

where $|| \cdot ||_2$ denotes the $L_2(P)$ norm. It follows that Assumption 5 guarantees $R_{11} = o_P(n^{-1/2})$. For R_{12}, we further suppress the dependency of $S_1(k \mid X)$, $G_1(k \mid X)$ and their estimators on both k and X, and rewrite the term as

$$R_{12} = E[\{\hat{e}(G_1 - \hat{G}_1) + G_1(e - \hat{e})\}\{\hat{\mu}_1(S_1 - \hat{S}_1) + S_1(\mu_1 - \hat{\mu}_1)\}/(\hat{e}\hat{G}_1)].$$

Because $\hat{e}/\hat{G}_1$ is bounded, by the Cauchy-Schwarz inequality, the first term in R_{12} is upper bounded by $||G_1 - \hat{G}_1||_2 ||S_1 - \hat{S}_1||_2 = o_P(n^{-1/2})$ by Assumption 5. The other three terms in R_{12} can be similarly bounded. Thus, $R_1(P, \hat{P}_n) = o_P(n^{-1/2})$.

Symmetric arguments imply the analogous term for the control arm satisfies $R_0(P, \hat{P}_n) = o_P(n^{-1/2})$. Therefore, the results in Theorem 4 follow from the central limit theorem. □